Volume 7 **Neurology** *Number 7*

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NEUROLOGY is published monthly at 84 South Tenth Street, Minneapolis 3, Minnesota, by LANCET PUBLICATIONS, INCORPORATED. Subscription rate: $12.00 a year, $1.00 a copy; outside the United States $13.00 a year, $1.10 a copy. Entered as second class matter at the postoffice at Minneapolis, January 23, 1951.

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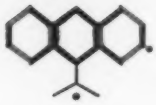

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Neurology Volume 7 • Number 7

The Cerebral Collateral Circulation

1. Factors Influencing Collateral Blood Flow

John S. Meyer, M.D. and D. Denny-Brown, M.D.

CLINICAL INVESTIGATION of syndromes due to atherosclerotic occlusion or stenosis of the internal carotid, middle cerebral, and basilar arteries has shown that many of the transient symptoms characteristic of such disorders are due to temporary failure of the cerebral collateral circulation. In a recent paper on this subject,[1] cerebrovascular insufficiency was defined as a state where the local or general blood flow was unable to maintain the metabolic requirements of the brain during physiologic stresses. Examples of stress situations commonly producing symptoms are reduction of cardiac output due to blood loss, postural hypotension, and cardiac dysrhythmia. The syndrome of cerebrovascular insufficiency was considered to be due to a discrepancy between supply of arterial blood and tissue demand for oxygen.

It is apparent that measures which tend to promote the development of the cerebral collateral circulation following occlusion of a cerebral vessel are of considerable therapeutic importance. The present study was undertaken to analyze factors influencing the efficiency of the cerebral collateral circulation as measured by means of the polarographic technic, to clarify the circumstances whereby collateral blood flow fails to prevent infarction, and to determine whether any aspects of infarction are reversible.

Experimental studies with the polarographic technic in monkey cortex[2–4] and later in man[5] have demonstrated the high oxygen consumption and small oxygen reservoir of healthy cerebral tissue. Early consequences of cerebral ischemia appear to be due to local hypoxic damage to neurons,[3,6] which may be reversible if a minimal blood flow is preserved. Cerebral anoxia results first in slowing of the electroencephalogram and later in an injury potential (S.P. shift). Once neuronal injury has occurred, the tissue demand for oxygen is greatly reduced, since metabolically paralyzed or infarcted brain has a minimal oxygen consumption.[1,2,5–7]

In experimental studies it has also been shown that the severity and duration of cerebral ischemia depends on the effective contribution of the collateral vessels.[3] Occlusion of the middle cerebral artery, for example, causes a severe reduction of cortical oxygen measurements in the distribution of the occluded vessel. There is a bordering zone in which the tissue oxygen is unstable and an outer zone in which the tissue oxygen and temperature rise, associated with the increase in the collateral circulation. The compensatory process appears to be independent of the sympathetic nervous system. The collateral circulation requires a minimum systolic blood pressure of 50 mm. of mercury; if the blood pressure falls below this, the collateral circulation fails. Prolonged occlusion of the middle cerebral artery in the presence of a low blood pressure results in infarction.[2,8]

The present communication considers various stimuli which may be demonstrated to

From the neurological unit, Boston City Hospital, and the department of neurology, Harvard Medical School, Boston, Massachusetts.

With the technical assistance of Robert C. Struzziero.
These studies were aided by a contract between the Office of Naval Research, Department of the Navy, and Harvard University, NR 115-401, and by a grant from the National Institute of Neurological Diseases and Blindness, B-1044, 1956-1957.
Opinions expressed are those of the authors and do not necessarily represent those of the Department of the Navy.

affect collateral blood flow and attempts to analyze factors which improve or impair the mechanism of compensation. A subsequent communication[2] describes the nature of damage to cerebral neurons and blood vessels resulting from failure of the collateral circulation and in what way certain aspects of the damage appear to be reversible.

MATERIALS AND METHODS

The present investigation was carried out on 33 monkeys (Macacus mulatta). Occasionally, reference was made to the protocols of 180 earlier experiments on related aspects of the cerebral circulation. Records of cortical oxygen availability of several small areas of the brain were made by a modification of the polarographic method described by us in previous studies.[3, 4–6, 9]. The principles of the electropolarographic method requires that a constant potention of 0.6 volts be supplied to a nonpolarizable anode by a potentiometer. The current flow between the anode and a platinum cathode is proportional to the oxygen available to the electrode tip. The platinum cathode is insulated with Teflon and 1 to 3 mm. of its tip is exposed. The electrodes are then calibrated equally in saline. In this series of experiments each EPG electrode had an independent battery, potentiometer, and silver-silver chloride anode. Since the oxygen availability of freshly infarcted brain is extremely low, it was thought that changes in the impedance properties of the infarct might cause artifactual increases in electrode readings of the bordering zone. This appears to be an unnecessary precaution, since the electrode readings were similar to those obtained with a common current source and anode.

Providing the cerebral metabolic rate and the oxygen content of the systemic circulation remain constant, changes in EPG oxygen in small areas of cerebral cortex have been shown to reflect local changes in blood flow.[3–6, 9] The electrocorticograph (EEG) and steady potential (S.P.) from the same areas of cortex were recorded as an index of neuronal activity. The reference S.P. electrode was placed in a homologous area of cortex in the opposite hemisphere. The femoral blood pressure (B.P.) was recorded continuously. Other relevant measurements were made in various combinations in order to clarify various aspects of the problem. Sensitive microthermistor beads (T) placed on cortical arteries indicated changes in blood flow.[4–6] In the present series of experiments, frequent observations and micrometer measurements were made of the pial vessels. In some experiments, measurements of their caliber and the appearance of the flow were dictated by one observer and noted on the record by hand; in later experiments color photomicrographs were taken at frequent intervals. The technic for photomicrography of the cortical vessels was similar to that described by Forbes.[10] A window was not used, but the cerebral hemisphere was exposed by a wide craniectomy and the brain was covered by a thin layer of mineral oil warmed to body temperature. The head was firmly held in a McGill head holder and the brain transfixed within the skull by a fine steel needle. Illumination of the microscopic field was provided by a filament lamp of the "Point-O-Lite" type filtered through cold water. Measurements of vascular caliber (CAL) were made by an ocular micrometer scale and a stereoscopic dissecting microscope having a magnification of 30 to 70 times, mounted on an adjustable arm. In addition, photomicrographs were taken of the same field with a Leica camera using either a 20 mm. or 48 mm. Microtessar lens fitted to an adjustable tube of approximately 30 cm. in length. This photomicrographic technic permitted magnification of 25 to 75 times.

The electrocorticograms (EEG) and steady potentials were recorded with silver-silver chloride electrodes. In many of the early experiments, electrocorticograms were recorded separately on a Grass electroencephalograph, but in later experiments AC and DC potentials were recorded concurrently on an 8 channel Offner electroencephalograph. This modification of the apparatus permitted an ink-writer polygraph to be substituted for the kymographic camera used in earlier experiments.[3, 4] The cortical oxygen availability (EPG) was also recorded in later experiments with the ink-writer. When the electrocorticogram was recorded with the ink-writer, the platinum electrode was connected to the positive pole of the potentiometer through a resistance of 47,000 ohms. On either side of this, resistance leads were taken to the D.C. amplifier after calibration with a vacuum tube microammeter.[5] This type of EPG recording permits a frequency response of 1/120th of a second. More rapid transient changes may be recorded than by the slower responses of the galvanometer.

Jugular, intracranial, and blood pressures were recorded with sensitive strain gauges.[4] Changes in pH of localized areas of cortex were measured with a microglass pH electrode.[4, 11]

Fine silk ligatures were placed around the common carotid arteries or the proximal and distal portion of the middle cerebral artery with a small curved needle, using a similar operative approach to that described by Rasmussen and Harvey.[8] Electrodes were then placed on the cortex and measurements and photographs of the cortical vessels were made. Each artery was occluded for varying lengths of time by gentle traction on the ligatures. In some experiments the cortical branches of the middle cerebral artery were occluded with silver clips during observation, without previous exposure of the carotid artery or the middle cerebral artery in the Sylvian fissure. Alteration of blood pressure was accomplished by several methods, including lowering and raising the feet on a small tilt-table, removal and reinjection of venous blood, and the use of adrenalin. In addition, the effects of breathing 100 per cent nitrogen before and after vascular occlusion were observed. The gas mixture was administered by a tracheal tube. A saturated solution of Trypan blue was injected in divided doses depending on the weight of the animal and the duration of the experiment, in order to provide information on vascular damage.[12,13]

At the completion of each experiment, the carotid arteries were injected with India ink and the vascular pattern of the vessels sketched on a diagram. The brain was then removed, fixed in formalin, and representative blocks were prepared for histologic examination.

RESULTS

General Observations

Polarographic records obtained with the ink-writer were similar to those obtained with the galvanometers, except that at high amplification small, rapid fluctuations (less than 4 per cent) of oxygen tension occurred, having the same frequency as the electrocorticogram and disappearing when the electrocorticogram became isoelectric. These may represent fluctuations in neuronal oxygen metabolism related to neuronal rhythmic activity or possibly are superimposed artifacts.

When the middle cerebral artery was occluded, pulsations of its branches emerging from the Sylvian fissure ceased. Active circulation continued in these vessels and they did not collapse. There was a rapid, severe reduction in cortical oxygen tension in the Sylvian region, which frequently remained at low levels, with less rapid and complete compensation than is seen when the carotid artery is occluded. Calibrated measurements of the oxygen availability of numerous areas of the cerebral hemisphere after application of a silver clip to the middle cerebral artery showed lowest oxygen readings in the temporal, parietal, and frontal operculae, being 5 to 20 per cent of normal. In surrounding zones oxygen values were higher in a patchy and irregular fashion. In the parasagittal and occipital zones the readings were usually 10 to 20 per cent higher than prior to occlusion. Microscopic examination of the vascular architecture revealed that, in the patchy, intermediate zone, those areas showing relatively higher oxygen readings were near an anastomotic vessel from the anterior or posterior cerebral arteries. In the parasagittal and occipital zones, where the readings were above baseline, the electrodes were in the proximal distribution of the same collateral vessels.

There was found to be a great deal of variability in the topographic supply of the middle cerebral artery in the monkey. In some animals the entire lateral surface of the hemisphere was supplied by the middle cerebral artery, while rarely in others the anterior and posterior cerebral arteries supplied most of the lateral hemisphere except for the lips of the Sylvian and central fissures. The size of arteries emerging from the Sylvian fissure was a reliable indicator of the variation. A comparable variability has been reported in the collateral circulation provided by the circle of Willis in the monkey.[3] Rarely a profound degree of cortical hypoxia resulted from occlusion of the common carotid artery when posterior communicating arteries provided a poor collateral circulation, particularly if the blood pressure was low (figure 1). In spite of anatomic variations in different animals, occlusion of the parasellar portion of the main trunk of the middle cerebral artery regularly caused a critical degree of hypoxia in the opercular cortex.

Occlusion of the artery more laterally as it emerged from the Sylvian fissure, after some branches have left the parent trunk, resulted in a less predictable and more reversible degree of cortical ischemia in the smaller area of supply. Providing the blood pressure was well maintained, the cortical tissue oxygen usually regained previous levels, but a fall in blood pressure was deleterious to the mechanism of compensation.

Changes in Intraluminal Pressure as a Local Vasodilator

The effect of changes in intraluminal pressure was well shown by cutting a small vessel,

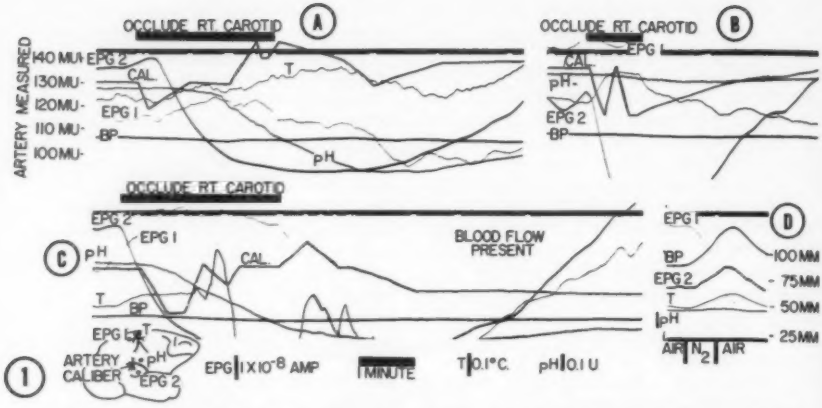

FIG. 1. Monkey. Nembutal and Thorazine anesthesia. Four samples from the same experiment. In this animal at necropsy the posterior communicating arteries were unusually small. *A*, *B*, and *C* were three occlusions made one after the other. In *C* the systolic blood pressure fell below 50 mm. mercury, resulting in failure of the collateral circulation, with ischemic neuronal paralysis localized to the Sylvian area (EPG 2) but without vascular thrombosis. An unusual transient disturbance of the T electrode in *C* was unexplained. *D*. Nitrogen breathing now produced a fall in EPG oxygen in the undamaged region (EPG 1) but not in the area of neuronal injury (EPG 2). Position of the electrodes is shown in diagram below record *C*, calibration of time intervals, EPG, T, and pH electrodes are shown at the bottom of illustration. Blood pressure calibration is shown in millimeters of mercury to the right of *D* and vascular diameter measurements for all records are shown at the left of *A*. In record *B* the unmarked galvanometer trace is the cortical temperature (T). Initial reading of EPG 2 = 10×10^{-8} amps.

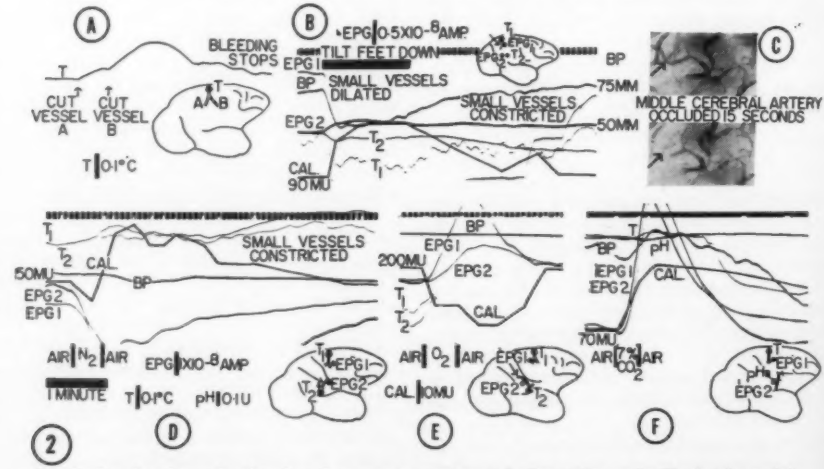

FIG. 2. Samples of records taken from five separate experiments in the monkey under Nembutal anesthsia to show the effects of changes in intraluminal pressure, oxygen tension, and carbon dioxide on local blood flow. In *A* two branches of the anterior cerebral artery (marked A and B on the diagram) were cut producing an increase in blood flow (T) in the proximal stump. In *B* a reduction of blood pressure caused an increase of the diameter (CAL) of a branch of the anterior cerebral artery. In *C* the two photomicrographs of a cortical arterio-arterial anastomosis show collapse of the vessel, indicated by the arrow, when the middle cerebral artery is occluded. *D* shows an increase in the diameter of a cortical artery when nitrogen was breathed, and *E* shows vasoconstriction when 100 per cent oxygen was breathed after air. In *F* breathing 7 per cent carbon dioxide and O_2 produced vasodilatation. See text. T = microthermistor, EPG = polarograph electrode, CAL = micrometer measurements of diameter of artery, pH = micro pH electrode, B.P. = femoral blood pressure. Brain diagram shows position of electrodes. Calibration of each electrode is shown at base of record and time interval indicates one minute.

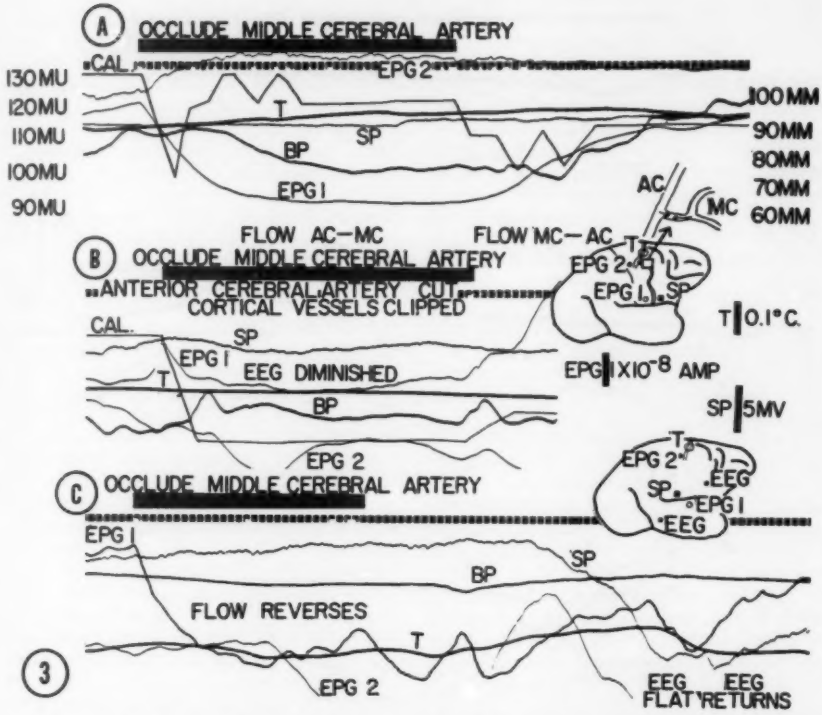

FIG. 3. Monkey (two experiments). Records *A* and *B* are from the same experiment. *A* illustrates an increase in collateral circulation (CAL, T, and EPG 2) from the anterior cerebral artery when the middle cerebral artery is briefly occluded. Occlusion of the anterior cerebral artery and other cortical vessels in B abolished the collateral blood flow when the maneuver was repeated. Occlusion of the middle cerebral artery in *C* resulted in severe hypoxia in the temporal cortex (EPG 1). The collateral circulation was delayed and incomplete (T and EPG 2). A transient injury potential and localized EEG suppression occurred despite release of the vessel. Electrode positions are shown on brain diagrams. A typical anastomosis between middle cerebral (MC) and anterior cerebral (AC) is drawn on record *A*. Arrows indicate changes in direction of flow noted on record as "AC-MC" and "MC-AC." Flow reversal also occurred in record *C*. Initial EPG 1 reading in figure *A* was 8×10^{-4} amps. and 6×10^{-4} amps. in figure *B*.

which produced a maximum fall in the intraluminal pressure. Section of a branch of the anterior cerebral artery, while observing the vessel with a microscope and also recording changes in flow with microthermistors placed on its wall, resulted in abrupt but temporary segmentation of the blood flow in the distal portion of the cut vessel, with brief constriction of its wall. As soon as the vessel was cut the proximal stump showed an increased blood flow, and when a second branch was cut there was a further increase in flow (figure 2A). When the cut ends of the vessels clotted, the bleeding ceased, blood flow decreased in the proximal stump, and rapid flow was seen to resume in the branches of the distal end, now entirely derived by way of collateral vessels. The reverse procedure of occluding the cortical vessel with a silver clip resulted in a small decrease in blood flow in both proximal and distal segments, but microscopic observations showed that rapid flow was resumed by way of the collateral vessels after 20 seconds. Such simple alterations in blood flow appear to be mediated by hemodynamic adjustments from high to low pressure areas. The rapidity of response bears no relation to any measurable change in metabolism of tissue. In figure 2C the arrow in the upper photomicrograph shows a small cortical arterio-arterial anastomosis between two branches of the middle cerebral artery. In the lower picture one arm

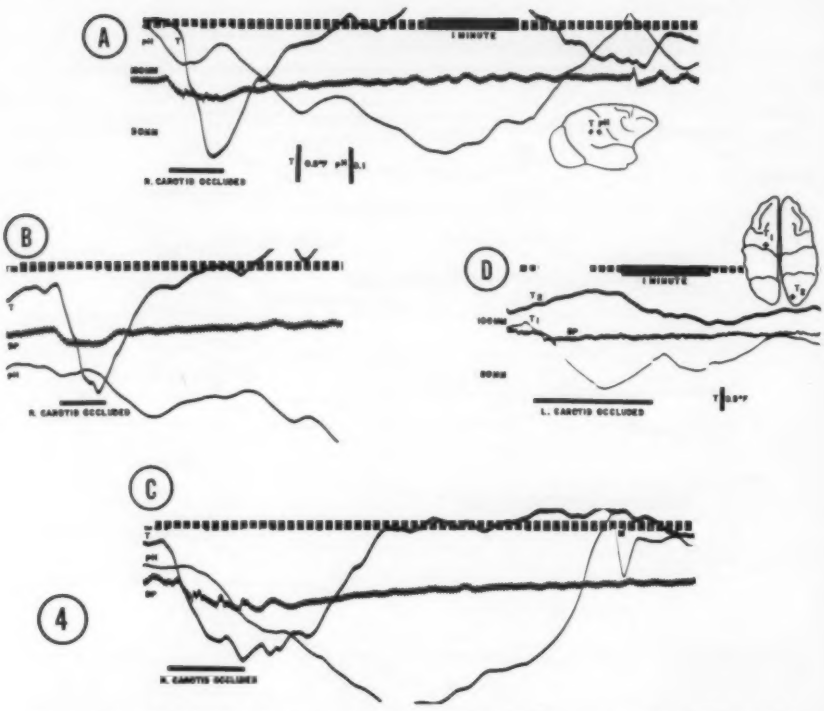

FIG. 4. Monkey. Nembutal anesthesia. *A, B,* and *C* are three records from the same experiment to show relation of increased cortical temperature to changes in cortical pH when the right carotid artery is occluded. *D* is a record from another experiment to show an increase in right occipital temperature when the left carotid artery was occluded. At M in figure *C* the pH galvanometer was lowered onto the record. Cortical temperature, pH, and blood pressure calibrations are noted on records. Time marker at top of record indicates six second intervals.

of the anastomosis measuring 110 mm. has collapsed 15 seconds after oclusion of the middle cerebral artery because of a virtual arrest of local circulation. Ten seconds later, in spite of continued occlusion, normal flow resumed in the vessel, now derived from anastomoses with the anterior cerebral artery. In figure 3A microscopic observations of an arterio-arterial anastomosis between the middle and anterior cerebral artery showed a reduction of caliber (CAL) for 24 seconds after occlusion of the middle cerebral artery, followed by a fluctuating return toward its normal size during the period of occlusion. As the caliber increased, a reversal of flow could be observed in the anastomosis, the flow now being from anterior to middle cerebral artery. Release of the middle cerebral artery resulted in a sudden reduction in caliber of the anastomosis; the flow reversed again and resumed the original pattern. Similar alterations in direction of flow were also observed in the anastomosis photographed in figure 2C.

A small reduction in the intraluminal pressure of cerebral vessels appears to result in their active dilatation, similar to that described in the limb vessels by Bayliss.[15] The explanation is that the smooth muscle of cerebral vessels, like other smooth muscle, responds to stretch by contraction. Reduction of intraluminal pressure, therefore, results in some degree of relaxation of contraction of the vessel wall. It is proposed to term dilatation of a vessel due to change in intraluminal pressure the "Bayliss effect," and it appears from this study to be the most potent single factor in local regulation of cerebral blood flow. In figure 2B, for example, a sudden reduction in

blood pressure from 75 to 50 mm. of mercury resulted in a temporary reduction of flow in the larger arteries (T_1, T_2, EPG 1), but there was a significant increase in the caliber of a small branch of the anterior cerebral artery that was being constantly measured. EPG 2 was placed in the terminal vascular net of the same vessel and showed a small rise, presumably consequent upon decreased peripheral vascular resistance. When the blood pressure was restored, the vessels constricted. Spasm of cerebral vessels induced by a greatly increased intraluminal pressure has been described by Byrom[13] in experimental hypertension. Rapid adjustments in cortical blood flow were recorded, with temperature electrodes placed on either hemisphere during occlusion of the common carotid artery. For example, in figure 4D an increase in blood flow in the right occipital region resulted when the left carotid artery was occluded. These adjustments are presumably mediated by changes in intraluminal pressure in the circle of Willis.

Local reactions of the arterial wall to changes in the head of pressure fail if the intraluminal pressure is reduced critically. Apparently a minimal head of pressure is necessary; otherwise segmentation of flow and vessel collapse occur. This may be seen in circulatory shock following rupture of a large cerebral vessel.

The local regulatory function of the intraluminal pressure is well demonstrated by serial clipping of the cortical vessels to a given area while concurrently recording their contributions microscopically and with temperature and EPG electrodes. As the first cortical vessel is clipped, rapid flow is restored within seconds from neighboring collaterals and the EPG and T electrodes show little if any fluctuations. As additional vessels are clipped, circulatory adjustments from the remaining collaterals become progressively delayed and fluctuations in EPG and T electrodes are more pronounced (figure 5). Finally, when all the visible cortical vessels supplying a small area are clipped, the oxygen tension is reduced and the electrocorticogram from that area becomes isoelectric. However, a sluggish flow derived from subcortical anastomoses is still visible.

The Bayliss effect appears to be independent of cortical metabolism since it continues to be demonstrable, providing severe infarction does not occur, after the electrocorticogram is isoelectric and an injury potential is present. Local adjustments in the collateral circulation also occur during hypothermia when cortical metabolism is minimal.[9]

Changes in intraluminal pressure appear to exert important regulatory effects within the first 30 seconds, but there is evidence that other factors exert a supporting influence on homeostasis of the cerebral circulation. When a vessel is occluded it is common to observe increases in the collateral blood flow continuing for many minutes or hours thereafter. These delayed adjustments in collateral blood flow were now examined in terms of any relation they might bear to localized changes in oxygen tension, the accumulation of acid metabolites, or tissue injury.

Reduction in Cortical Oxygen Tension as a Local Vasodilator

In figure 2D the effect of breathing 100 per cent nitrogen for 30 seconds is shown on the diameter of a branch of the anterior cerebral artery measuring 150 mu. During nitrogen breathing the diameter (CAL) of the vessel was increased by 30 mu and the local blood flow as measured by microthermistors (T_1, T_2) also increased in a parallel manner. The vasodilatation followed inversely the reduction in local cortical oxygen tension indicated by the EPG electrodes (EPG1 and 2) placed near the artery. Conversely, breathing 100 per cent oxygen (figure 2E) resulted in reduction of the diameter of a 200 mu cortical arteriole and a similar reduction on local blood flow (T_1, T_2). This vasoconstriction was also inverse to

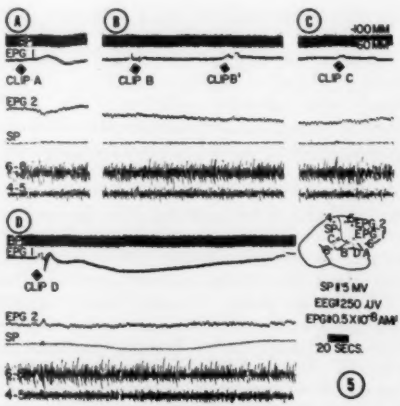

FIG. 5. Four strips of record from the same experiment to show the transient effect of applying multiple clips to cortical arteries. In *D* when the fifth vessel was clipped, EPG 1 shows a brief reduction of oxygen availability and an associated SP shift. Electrode positions and cortical vessels are shown on brain diagram. Calibrations of EPG, SP, EEG, and time are marked to the right of record *D*, and BP at top of record *C*.

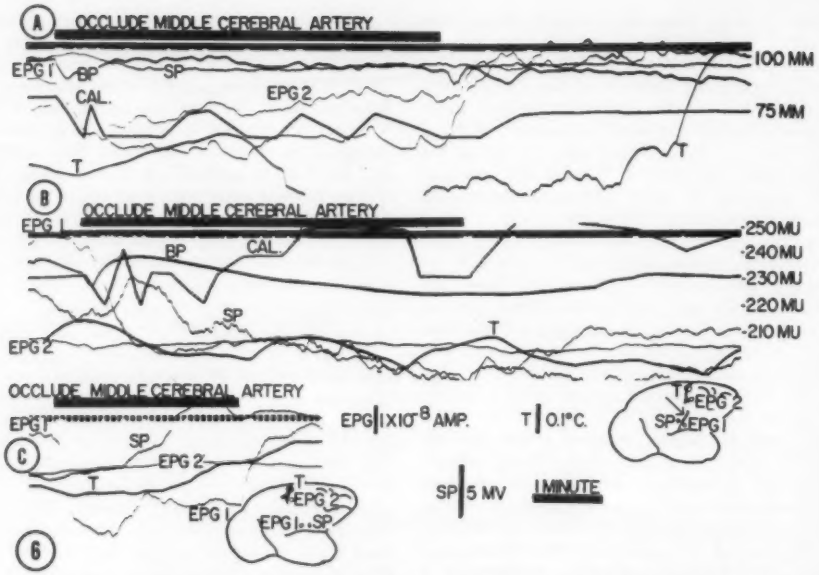

FIG. 6. Monkey (two experiments). Records *A* and *B* illustrate repeated occlusion of the middle cerebral artery with a poor rise in EPG 2 and T which represent the collateral circulation. In presence of low BP, the second occlusion in *B* results in severe cortical hypoxia, dilatation of the middle cerebral artery (CAL), and an injury potential (S.P.). *C* is a record from another experiment showing an injury potential (S.P.) associated with a rise in the oxygen tension in the ischemic territory (EPG 1), presumably due to lowered neuronal oxygen consumption produced by injury. In record C the injury potential is indicated by an upward deflection instead of downward, as in the other records.

the increase in local oxygen availability (EPG 1 and 2).

Comparable degrees of cortical hypoxia to those produced by nitrogen breathing are commonly seen following occlusion of the middle cerebral artery and occasionally after occlusion of the common carotid artery. In figure 1A a delayed secondary increase in the collateral blood flow independent of the Bayliss effect occurred one to two minutes after the common carotid artery was occluded, as shown by measurements of vascular diameter (CAL) and blood flow of the anterior cerebral artery (T). This secondary increase usually appears with prolonged occlusion of a vessel but not with brief occlusion of less than one to two minutes (figure 1B). The functional importance of local regulation of the collateral blood flow was shown by the experiment illustrated in figure 6A and B. In figure 6A occlusion of the middle cerebral artery for six minutes at a systolic blood pressure of 100 mm. of mercury resulted in a relatively small fluctuant fall in EPG 1 with a delayed increase in the collateral blood flow (EPG 2) and a rhythmic rise in the Sylvian region (EPG 1). The collateral blood flow (T) from a large cortical branch of the anterior cerebral artery was irregular and poorly sustained. The artery was again occluded for six minutes, as shown in figure 6B, at a systemic blood pressure of 85 millimeters of mercury. The collateral circulation now failed to increase (T and EPG 2), resulting in severe cortical hypoxia in the distribution of the middle cerebral artery (EPG 1) and the development of an injury potential. The small (200 mu) branches of the middle cerebral artery dilated, presumably due to local hypoxia and acidity, but in spite of this the collateral circulation was inadequate to maintain the demand for oxygen. Several minutes after the middle cerebral artery was released, there was recovery of the cortical blood flow as judged by temperature and EPG electrodes and the injury potential reverted back to the steady state.

Reduction in Cortical pH as a Local Vasodilator

It has been shown previously that carbon dioxide acts as a vasodilator on the cortical

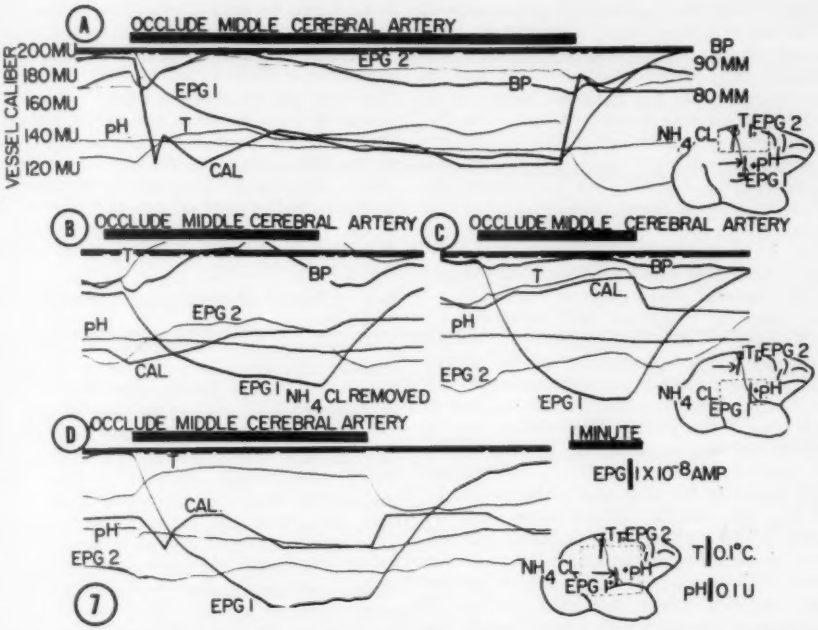

FIG. 7. Monkey. Four records from the same experiment to show the effect of application of NH_4Cl solution (pH 0.6) to the areas of cortex outlined by broken lines on the brain diagrams. The ammonium chloride was removed 30 minutes before record *B* and reapplied in the new area before record *C*. The effective collateral circulation is not significantly changed except that in *A* cortical arteries are widely dilated prior to occlusion when acid is applied.

In records *A*, *B*, and *D* the middle cerebral artery was measured; in *C* the anterior cerebral artery was observed. Electrode and time calibrations shown at right lower corner, blood pressure (B.P.) calibration to right of *A*, and arterial diameter measurements in micra are noted to left of *A*. Initial EPG 1 reading is 10×10^{-8} amps.

arteries of the monkey.[4] The vasodilator effect of breathing 7 per cent carbon dioxide after air is illustrated in figure 2F, where there was an increase in the caliber of a 70 mu arteriole by 40 per cent, associated with a rise in cortical temperature (T) and a reduction in cortical pH. This vasodilator effect of carbon dioxide occurred in spite of the competitive influence of an increase in cortical EPG oxygen (EPG 1 and 2) which would tend to exert a vasoconstrictor action. In such a situation the changes in carbon dioxide tension overrule those of oxygen in the control of the cortical circulation.

Acid Metabolites

In figure 1A prolonged occlusion of the carotid artery produced a localized decrease in the pH of the post-central gyrus by 0.5 pH units. The associated increase in caliber of a neighboring artery measuring 130 mu is presumably due in part to the local reduction in cortical pH and oxygen tension. Brief occlusion of the carotid artery, as in figure 1B, illustrates the dominant action of changes in cortical pH over those occurring in oxygen tension. Ischemia for one minute or less caused a transient but considerable degree of local cortical hypoxia without significant change in pH. More prolonged occlusion caused a marked cortical acidity and a greater degree of local vasodilatation.

The relative importance of pH as a stimulus for local adjustments in the collateral circulation is clarified by analysis of observations made during the supernormal or "rebound" phase that occurs when an occluded vessel is released. The local oxygen tension and cortical temperature promptly rise above baseline and persist there for from one to five minutes, depending on the severity of the ischemia, before returning to the steady state. This phenomenon has been discussed in detail else-

where.[3–6] and the supernormal phase appears to be due to a local reactive hyperemia. Presumably the collateral vessels surounding the ischemic zone remain dilated for as long as five minutes after the occluded vessel is released. The reactive hyperemia cannot be due to reduction in intraluminal pressure, since this is promptly restored to normal when the occluded vessel is released. As the cortical oxygen tension rises above baseline during this period, the rebound phenomenon is not mediated by oxygen lack. A more consistent inverse relationship exists between local pH and the supernormal phase (figures 1 and 4).

In order to determine the importance of local acidity in controlling adjustments in local blood flow following occlusion of the middle cerebral artery, cotton pledgets soaked in 0.8 per cent ammonium chloride were applied to small areas of the cortex. The solution, having a pH of 0.6, was warmed to body temperature and applied for five minutes to the various areas shown in the diagrams of figure 7A, C, and D. The middle cerebral artery was occluded before and after the solution was applied. Application of the acid solution to the cortex resulted in an increased diameter of the small arterioles (100 to 200 mu), not only in the region where the solution was applied but also in neighboring anastomotic vessels. For example, application of the pledget to the territory of the anterior cerebral artery caused dilatation of the anastomotic branches of the middle cerebral artery and vice versa (figure 7A and C). The application of the acid solution to the territory of the anterior cerebral artery alone lessened the degree of ischemia in the territory of the middle cerebral artery (figure 7A), whereas application to the middle cerebral alone did not alter the degree of ischemia (figure 7C and D with 7B).

Products of Tissue Damage as a Local Vasodilator

If occlusion of a cerebral vessel is followed by failure of the collateral circulation, resultant local ischemia produces a reversible degree of neuronal injury without necessarily injuring blood vessels.[1–3,6] The severity of neuronal injury correlates with the degree and duration of cortical hypoxia. The first abnormality resulting from ischemia is slowing and altered amplitude of the electrocorticogram in the territory of supply. Continued ischemia eventually results in a local injury potential (figures 3C, 6C, and 8), which is associated with functional impairment of the neurons.[6] These experiments have not demonstrated any metabolic factor in injury, other than those causing local acidity, that appears to significantly alter the adjustment of the cerebral collateral circulation. There is, for example, no correlation between the onset of injury potential induced by local ischemia and any alteration in the bordering blood flow. Occasionally a rise in the EPG oxygen in the ischemic zone correlates with the development of the injury potential from the same area as in figure 6C, but in this case it was believed to result from reduced neuronal metabolism associated with the injury.

Size of Vessels Mediating the Collateral Blood Flow

Microscopic observations indicate that most marked alterations in caliber occur in arterial vessels of the 50 to 250 mu size, where changes in diameter may amount to over 50 per cent (figure 2). Larger vessels show less remarkable changes in diameter and the main arterial trunks seldom show alteration in size. Microthermistors placed on large vessels show that changes in flow may occur without alteration in vascular diameter. When a large cerebral vessel is occluded, the most active adjustments in flow are seen in the arterio-arterial anastomoses between main cerebral vessels measuring between 50 and 250 mu and comparable to the meningeal arterial anastomoses described in man.[16,17] It is in these vessels that slowing, flow reversal, and rapid increases in the circulation can be most readily seen under the microscope.

DISCUSSION

Analysis of the adjustments in the collateral circulation following occlusion of various cerebral vessels shows that functionally important anastomoses exist between cerebral arteries of all sizes from the terminal arteriolar net to the circle of Willis. The most important factor controlling adjustments in the collateral vessels appears to be the intraluminal pressure. A localized reduction in intraluminal pressure results in dilatation of the vessel and an increased flow from neighboring collaterals having a higher head of pressure. This phenomenon is particularly striking in the small cortical arterioles of 50 to 250 mu in size where hemodynamic adjustments such as complete reversal of flow, changes in the rate of flow, and alteration in vascular diameter can be seen with the microscope.

The phenomenon of alteration in vascular diameter mediated by the local head of pressure we term the Bayliss effect, and this ap-

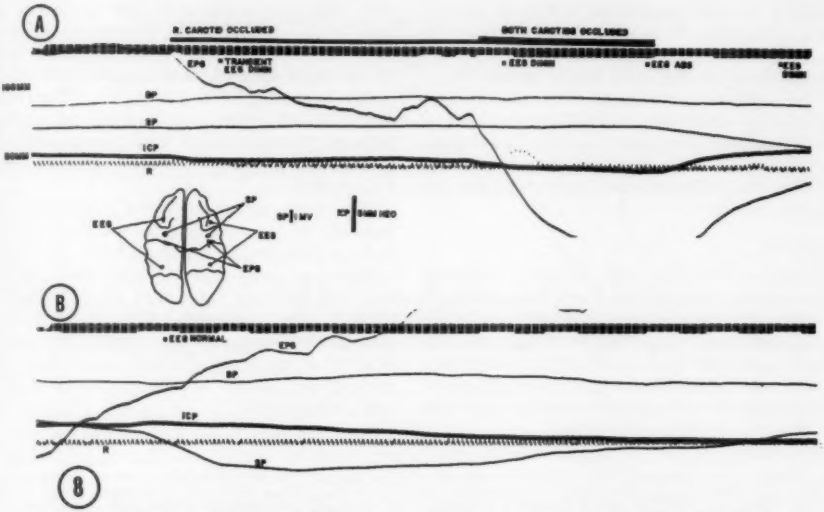

FIG. 8. Monkey, light Nembutal anesthesia. *B* is a continuation of record *A*, to show relation of changes in cortical oxygen availability (EPG) to EEG, steady potential (S.P.), and intracranial pressure (I.C.P.). Femoral blood pressure (BP) and respirations (R) are also recorded. There was an unusually poor collateral circulation from the posterior communicating arteries in this animal. Occlusion of the right carotid artery resulted in a reduction of the cortical EPG readings from 13×10^{-6} amps. to 10×10^{-6} amps. with an irregular rise toward baseline. Occlusion of both carotid arteries produced a severe fall in the cortical EPG to 6×10^{-6} amps. The EEG and S.P. show evidence of neuronal injury. The intracranial pressure is reduced when one carotid is occluded but shows a rise after 20 seconds. When both carotids are occluded, the intracranial pressure is further reduced and there is no increase prior to release of the vessels. When the vessels are released, there is a marked increase in intracranial pressure. Blood pressure calibration is to the left of *A*. Time marker indicates six second intervals.

pears to cause rapid compensatory changes within the first 30 seconds. Thereafter, slower circulatory adjustments occur that appear to be mediated by a number of metabolic factors acting in combination. Some measure of such factors has been determined in the present study and is found to include reduction in local oxygen tension and the accumulation of acid metabolites and carbon dioxide. As measured within the first few minutes after occlusion, their influence is relatively unimportant compared with the Bayliss effect, but it is probable that their influence is more significant over periods of hours or days. In the human brain a progressive increase in the collateral circulation has been demonstrated to occur in the ensuing seven days following gradual occlusion of the internal carotid artery, but the factors concerned in such delayed effects have not been further defined.[9]

While it seems probable from these studies that localized hypoxia resulting from vascular occlusion contributes to the adjustment in collateral blood flow, this contribution is probably a minor one since we have found that the compensatory process is still present whether 100 per cent or 7 per cent oxygen is breathed prior to occluding a cerebral vessel. In the same way, we have found that adjustments in the collateral circulation continue after prolonged inhalation of a mixture of 10 per cent carbon dioxide in air[3] and conclude that carbon dioxide, like oxygen, plays a minor role in the regulation of the cerebral collateral circulation.

Localized accumulation of acid metabolites appears to be a more significant contributing factor in the control of the collateral blood flow and appears to be responsible for a large part of the reactive hyperemia occurring after prolonged ischemia. This cortical acidity only ensues after prolonged and severe vascular occlusion and is probably due for the most part to ischemic neuronal damage, since a similar acidity occurs following prolonged respiratory anoxia and is associated with a reactive hyperemia.[6] Furthermore, the application of an acid solution to the area of anastomotic supply does alter the effective collateral blood flow. The elaboration of other "histamine-like" substances

exerting a local vasodilator action in the ischemic territory is possible, but we have no well defined evidence of such a factor in the development of the local injury potential.

The cerebral circulation is remarkably efficient in the presence of a well maintained systolic blood pressure, but when the blood pressure falls below a critical level of 50 mm. of mercury the collateral circulation fails and infarction results.

SUMMARY

Factors influencing the cerebral collateral circulation in the monkey have been analyzed in terms of local changes in oxygen availability, temperature, pH, electrocorticogram, and steady potential (S.P.). These measurements were made while observing any change in the pial circulation. Adjustments in collateral blood flow following cerebrovascular occlusion appear to be mediated by vessels of all sizes, from the large vessels of the circle of Willis to the small arterio-arterial anastomoses of the cortex measuring 50 to 250 micra. These small arterial anastomoses form multiple connections between arterial trunks and permit wide readjustments in local blood flow when an artery is occluded.

The most important factor controlling adjustment of the collateral blood flow appears to be a reduction in the local head of pressure resulting in vasodilatation. Such local changes in blood flow are rapid and occur within 30 seconds after occlusion. Delayed circulatory adjustments appear to be mediated by a combination of factors, including reduction in oxygen tension and the localized accumulation of acid metabolites.

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Statistical Control Studies in Neurology

8. The Cutaneous Abdominal Reflex

M. J. Madonick, M.D.

DIVERGENT FIGURES have been reported regarding the incidence of absence of the cutaneous or superficial abdominal reflexes in healthy people and in various physiologic and pathologic states. Large control studies have been few. In the present investigation two groups, one of non-neurologic admissions to a general hospital and one of a large series of psychoneurotic patients, have been examined to determine the incidence of absence of the cutaneous abdominal reflexes and the possible correlation with various states.

Rosenbach described the cutaneous abdominal reflex in 1876.[1] It was elicited by stroking the abdominal wall transversely or parallel to the midline, either with the fingernail or handle of the percussion hammer.[2] A contraction of the abdominal wall was produced. He noted its absence on the paretic side of hemiplegics and explained its absence as due to interruption of the corticospinal pathway. Rosenbach, in the examination of a large but unstated number of healthy individuals, obtained the reflex in every instance. Kupferberg[3] examined 36 patients, most of whom had pulmonary tuberculosis, pulmonary emphysema, or arthritis but without neurologic disorders. The cutaneous abdominal reflexes were absent bilaterally in four instances; three of these patients were over 40 years of age. Geigel[4] found the cutaneous abdominal reflex absent in 8 per cent of 88 women, and he referred to Plaesterer who examined 100 healthy men in whom the superficial abdominal reflexes were present in 99 per cent. Agostini[5] stated that the cutaneous abdominal reflexes were absent in 18 per cent of people. Dinkler[6] did not find the reflex absent in normal subjects. In Strümpell's[7] series of 185 people, the superficial abdominal reflexes were absent in 13.5 per cent. Bodon[8] stated that the cutaneous abdominal reflexes vary in the same subjects at different examinations. He found them absent in normal people. He considered it significant if one was weaker than the other. Schoenborn[9] found the cutaneous abdominal reflexes absent in 2 per cent of 100 men who had no neurologic disorders. Oppenheim[10] stated that in his experience the superficial abdominal reflexes were absent "in 15 to 20 per cent of healthy individuals." Unfortunately, the number of people examined was not indicated. In his textbook[11] he wrote that this "reflex is inconstant in health." Müller[12] stated that the cutaneous abdominal reflexes are absent in about 5 per cent of normal people below the age of 50, more often absent in women than in men. Müller and Seidelmann[13] examined 1,000 normal soldiers and the superficial abdominal reflexes were absent in only one; in 2,000 non-neurologic female patients with firm abdominal walls and intact internal organs, they were not absent in even one. Söderbergh,[14] in his series of 700 patients between the ages of two and a half and 68 years, found the upper cutaneous abdominal reflexes absent in 0.6 per cent, the middle in 0.3 per cent, and the lowest in 0.7 per cent; in no instance was there complete absence of all three reflexes. Vertes[15] tested 1,000 soldiers between the ages of 20 and 50 years who were admitted to the hospital chiefly for respiratory disorders; the cutaneous abdominal reflexes were absent in 5.1 per cent on both sides and in all three zones; the reflex was absent in one of the three zones in 14.7 per cent of the soldiers. Bott[16] summarized Dosuzkove's results of the latter's 500 males between 21 and 60 years. There was absence of the epigastric, mesogastric, and hypogastric reflexes on one side in 1.8, 1.8 and 2.0 per cent, respectively; there was absence of the epigastric, mesogastric, and hypogastric reflexes on both sides in 1.8, 3.2, and 6.2 per cent of the cases, respectively. Van Rijnberk[17] referred to the work of Munch-Petersen; the latter found the cutaneous abdominal reflexes absent in 14⅛ per cent of 200 males and in 23 per cent of 200 females. Willach[18] examined 715 members of 200 Berlin families and the cutaneous abdominal reflexes were absent in 1.7 per cent; however, in the families of multiple sclerotics of comparable ages, the cutaneous abdominal reflexes were absent in 10 per cent. McAlpine[19] refers to a communication from Henderson who investigated the cutaneous abdominal reflexes in 844 students. Henderson noted "depression or even absence

From the neuropsychiatric service, Morrisania City Hospital, New York City.

of these reflexes was not rare in otherwise healthy young persons, particularly if examined in a cold room."

Jamin[20] found the abdominal cutaneous reflexes to be diminished or absent in acute organic disease of the abdomen more than in chronic abdominal disease. They were lost on the right side in perityphilitis, gallstone colic, and cholecystitis. Klein[21] studied 200 surgical cases. He found that in adults the absence of the superficial abdominal reflex differentiates intraabdominal from intrathoracic disease. If rigidity of the abdominal wall is not due to peritoneal irritation, then a response occurs; if it is due to peritoneal irritation, the cutaneous abdominal reflexes are absent. However, Williams[22] indicated that abdominal wall rigidity resulting from peritoneal irritation could not explain the absence of the cutaneous abdominal reflex in renal colic.

MATERIALS AND METHODS

Two groups of people were studied. Group 1 was composed of 2,500 patients with nonneurologic disease admitted to the surgical, medical, and obstetric wards of the Morrisania City Hospital. The age incidence of the group showed a bell-shaped curve when graphed, indicating that the sample was statistically valid. There were 1,695 females and 805 males. This ratio is greater than the ratio of 100.6 females to 100 males in the Bronx, according to the census of 1930. The greater number of females is due probably to the large gynecologic division of this hospital. Negroes comprise 1.02 per cent of the population of the county; of the series of 2,500 hospital patients, Negroes constituted 21.6 per cent of those examined. The greater number of Negroes in the series is most likely due to economic conditions and the fact that the hospital is a city institution. Group 2 was composed of 1,000 non-hospital patients suffering from various psychoneuroses, ranging in age from nine to 69 years.

Among the numerous methods employed in testing for the cutaneous abdominal reflexes have been the fingernail,[1] matchstick,[23] pin,[24] blunt pencil,[24,25] handle of reflex hammer,[2] metal rod,[26] electric pencil,[27] pin-wheel,[28] and ice.[29] The technic used in the present investigation was similar to that of Parisot.[30] The dull end of a pin was first employed as the testing object; if no response was elicited, then the sharp end of a safety pin was substituted. The direction of the stroke was transverse from the lateral margin inward and it was carried out quickly. Blum's[31] method of reenforcement was at times of value in bringing out the reflex.

In view of the present investigator's agreement with Walter's[32] statement that the middle cutaneous abdominal reflexes have little practical value, with the possible exception of contributing to localizing the levels in spinal cord disease, the superficial abdominal reflexes were classified as upper and lower abdominal on right and left sides, as introduced by Rosenbach,[1] equivalent to the supra- and infraumbilical reflexes of Oppenheim,[11] rather than the more complicated divisions favored by Söderbergh[14] or Monrad-Krohn.[24]

Monrad-Kohn[24] believes the abdominal cutaneous reflex is dependent on a long cerebral reflex arc which reaches up to the motor and sensory areas of the brain. He also thinks there is an inhibiting or controlling system represented by the rubrospinal tract. He emphasizes a differentiation between the normal cutaneous abdominal reflex, which is chiefly unilateral, with a more or less marked deviation of the umbilicus and the linea alba and ordinarily produced only by stroking from the pathologic abdominal reflex.[33,34] The latter he classified with spinal automatisms which are generally associated with other such reflexes (flexion or extension reflexes of the lower limbs) He states the pathologic abdominal reflex has a greater tendency to result in bilateral contraction, to have a prolonged period of latency, and to be independent of the pyramidal tract. Langworthy[35] indicated that the spinal reflex arcs are normally under the control of pathways from the brain. The result of this control is either augmentation or inhibition of the spinal reflex. Following injury to the corticospinal fibers, the cutaneous abdominal reflexes are decreased or abolished. Hence, influences from the motor cerebral cortex normally augment the abdominal cutaneous reflex. On the other hand, the motor cerebral cortex normally inhibits the tendon reflexes so that they become hyperactive after the pyramidal tracts are injured. Astwazaturow[36] was of the opinion that the cutaneous abdominal reflexes were dependent on a central reflex arc. Since they disappear in pyramidal tract lesions, he suggested that the cutaneous abdominal reflexes are newer phylogenetic acquisitions. They cannot be obtained in domestic animals. Lewandowsky[37] considered their absence a pyramidal tract sign. Wartenberg[38] wrote that "the importance of the superficial abdominal reflex lies in the fact that its loss is highly indicative of

a lesion of the pyramidal tract." He continued that "it must be remembered, however, that this reflex may also be absent in non-neurologic conditions and may be preserved and return in pyramidal lesions." Bychowski[39] failed to elicit the cutaneous abdominal reflex in the newborn; it was demonstrated in 41 per cent of the children examined between four and a half and ten months of age. DeAngelis[40] found the cutaneous abdominal reflex brisk in 16 per cent, hardly perceptible in 77 per cent, and entirely absent in 7 per cent of the newborns in his study. Astwazturow[36] stated that the cutaneous abdominal reflex appears at the eighth month at about the time the child assumes the sitting position. Skinner[26] found the appearance of the cutaneous abdominal reflex usually at the sixth or seventh month of life; its appearance occurs at the same time with the change in the plantar reflex, and the dependence of the latter on the maturity of the pyramidal corticospinal pathway also points to a recent evolutionary change causing the reflex.

In neuropathologic, surgical, and experimental investigations, a few findings have been noted dealing with the cutaneous abdominal reflex. Thus, Travis[41] found the abdominal cutaneous reflex to be absent for about two weeks, then impaired for an additional two to four weeks, on the side opposite to the removal of the precentral motor cortex in macaca mulatta. Tower[42] showed that section of the pyramids in the chimpanzee and monkey resulted in absent cutaneous abdominal reflexes. She stated that no recorded study of uncomplicated section of the medullary pyramids in man was known. However, in ten possible cases of such lesions the cutaneous abdominal reflexes were absent. Foerster[43] excised the precentral gyrus in man; the superficial abdominal reflexes were initially abolished but returned after seven to ten days. Bucy's[44] results were similar. Lassek[45] collected 16 cases which showed total loss of the pyramidal tract fibers in man; the cutaneous abdominals were absent in seven. That the superficial abdominals may be still present with lesions of the pyramidal tract is suggested by the presence of these reflexes clinically, in Little's disease as described by Wilson[46] and Lewandowsky,[47] in hemiplegia described by Nathan,[48] and in spastic paralysis and hemiplegia described by Yanowitz.[49] Pathologically, it is suggested by the retention of the cutaneous abdominal reflex in nine of the 16 cases collected by Lassek.[45] It is also confirmed by the case of Dejerine and Long[50] of complete transection of the cord at the seventh cervical segment. Complete and total destruction of the corticospinal tract both in its central and lateral divisions was found at autopsy; the cutaneous abdominal reflexes were present during the illness of this patient. The above case is somewhat against Skinner's[26] acceptance of the direct corticospinal tract as being the pathway concerned with the cutaneous abdominal reflex. Skinner referred to Cunningham, who indicated that the direct pyramidal tract does not appear in mammals until the anthropoid stage is reached. Since the cutaneous abdominal reflexes also appear only at the anthropoid level, it may be speculated that the cutaneous abdominal reflex depends upon the direct pyramidal pathway. About 15 per cent of human beings do not have a direct pyramidal tract so that further speculation could then account for the small number of people who, for no apparent reason, never seem to have the cutaneous abdominal reflexes.

Rossen, Kabat, and Anderson[51] induced cerebral anoxia experimentally by arrest of the cerebral circulation in 11 schizophrenics. The superficial abdominal reflexes were diminished or absent during this state. Usually the cutaneous abdominal reflexes had disappeared before the appearance of pathologic reflexes.

RESULTS OF STUDY

Rolleston[52] indicated that in healthy adult life the cutaneous abdominal reflexes usually remain active till the age of 50, after which they tend to disappear. In his study of these reflexes in typhoid fever, he wrote "the frequency, degree, and duration of impairment of the abdominal reflex are, as a rule, in direct proportion to the age of the patient." Moeli[29] stated that the cutaneous abdominal reflexes are inconstant in old people. Monrad-Krohn[24] found the cutaneous abdominal reflexes to be less constant in older people. Skinner[26] indicated that the cutaneous abdominal reflexes are more often absent in the older individual. Munch-Petersen's figures for the absence of the cutaneous abdominal reflexes, summarized by van Rijnberk,[17] were absent in 29 per cent up to two years, absent in 0.9 per cent between two to 30 years, absent in 20.4 per cent between 30 to 60 years, absent in 47.9 per cent between 60 to 90 years. Critchley[53] stated that the cutaneous abdominal reflex "may indeed be unobtainable as early in life as middle age." The present investigation shows a definite rise in the incidence of absence of the cutaneous abdominal reflexes with age (tables

TABLE 1

INCIDENCE OF ABSENCE OF CUTANEOUS ABDOMINAL REFLEXES WITH AGE AND SEX IN 2,500 HOSPITAL CASES

Age Group	Males and Females			Males			Females		
	No. of Males and Females	No. of Absent Abdominals	Pct. of Absent Abdominals	Number of Males	No. of Absent Abdominals	Pct. of Absent Abdominals	Number of Females	No. of Absent Abdominals	Pct. of Absent Abdominals
0 to 9	89	0	0	43	0	0	46	0	0
10 to 19	368	10	2.7	114	1	0.87	254	9	3.6
20 to 29	534	45	8.4	85	4	4.7	449	41	9.1
30 to 39	474	67	14.1	100	5	5.0	374	62	16.6
40 to 49	388	69	17.8	138	16	11.6	250	53	21.2
50 to 59	318	82	25.8	155	23	14.8	163	59	36.2
60 to 69	230	84	36.5	118	36	30.5	112	48	42.9
70 to 79	90	49	54.4	45	21	46.7	45	28	62.2
80+	9	7	77.7	7	5	71.4	2	2	100

1 and 2). Thus the cutaneous abdominal reflexes were absent in 10.3 per cent of patients under 50 years of age and in 34.5 per cent of those above 50 years of age in group 1. In group 2, the cutaneous abdominal reflexes were absent in 9.0 per cent of those below 50 years and in 13.0 per cent of those above 50 years of age, which constitute a significant difference. In the present study the right cutaneous abdominal reflexes were absent in 69.5 per cent, the left absent in 30.5 per cent of the unilateral cases. This is the reverse of Parisot's[30] results; he found the right-sided cutaneous abdominal reflexes to remain more so than the left. Lower abdominals were absent five times as often as uppers in the present study.

Müller[12] stated that the cutaneous abdominal reflexes are more often absent in women than in men. Strümpell[7] and Munch-Petersen[17] also showed a higher incidence of absence in females than in males. Klein[21] stated that the reflexes persist longer in males than in females. In tables 1 and 2 is shown the incidence of cutaneous abdominal reflexes according to sex in groups 1 and 2, respectively. The figures show a higher incidence of absence of the superficial abdominal reflexes in women than in men, 17.8 to 13.8 per cent in group 1, and 9.5 to 6.6 per cent in group 2. Table 3 is a résumé of tables 1 and 2.

In table 4 are shown the figures for absent cutaneous abdominal reflexes with other clinical evidence of neurologic involvement. The latter evidences were weakness in the limbs, changes in the tendon reflexes, and the elicitation of Babinski, Rossolimo, Gordon, Oppenheim, or Hoffmann signs. Thus, in group 1, of all patients with absent cutaneous abdominal reflexes, 21 per cent were associated with other evidence of nervous system involvement. From this table it is noted that, even in the age group of 70 to 79, absence of the abdominal cutaneous reflexes was associated in only 15 per cent of cases with other evidence of nervous system involvement. The diagnoses of cases of absence of cutaneous abdominal reflexes with and without other evidence of neurologic involvement are shown in table 5.

There is a difference of opinion regarding the cutaneous abdominal reflexes in the neuroses. Hedde[54] and Stern-Piper[27] stated that they sometimes disappear in the neuroses. Byrnes[23] and Goldflam[25] wrote that they were never abolished in these states. As seen in table 2, the cutaneous abdominal reflexes are absent in a fair per cent of neurotic patients; the figures are lower than in group 1. Lewandowsky[37] stated that they are often, if not

TABLE 2

INCIDENCE OF ABSENCE OF CUTANEOUS ABDOMINAL REFLEXES WITH AGE AND SEX IN 1,000 NEUROTIC PATIENTS

Age Group	Males and Females			Males			Females		
	No. of Males and Females	No. of Absent Abdominals	Pct. of Absent Abdominals	Number of Males	No. of Absent Abdominals	Pct. of Absent Abdominals	Number of Females	No. of Absent Abdominals	Pct. of Absent Abdominals
0 to 9	6	0	0	2	0	0	4	0	0
10 to 19	50	1	2.0	19	1	5.3	31	0	0
20 to 29	278	15	5.4	101	5	5.0	177	10	5.7
30 to 39	376	40	10.6	141	13	9.2	235	27	11.5
40 to 49	213	18	7.8	102	5	5.0	111	13	11.7
50 to 59	64	9	14.1	24	2	8.3	40	7	17.5
60 to 69	13	1	7.7	3	0	0	10	1	10.0

TABLE 3

SUMMARY OF FINDINGS OF CUTANEOUS ABDOMINAL REFLEXES

Absent cutaneous abdominals	*Group 1*	*Group 2*
In total number of cases	16.5%	8.4%
Below age of 50	10.3	8.0
Above age of 50	34.3	13.0
In males below 50	5.4	6.6
In males above 50	26.2	7.7
In females below 50	12.0	8.9
In females above 50	42.5	16.0
In all males	13.8	6.6
In all females	17.8	9.5
Bilaterally	92.3	82.0
Unilaterally	8.7	18.0

always, abolished in hysteria and in suggested anesthesia of the abdominal wall. Crouzon[55] indicated that they persist despite sensory changes in hysteria. To clarify this subject, 94 patients with hysteria, in addition to the post-concussion state, were examined 21 days to eight years after having sustained a head injury. These patients had midline hemisensory syndromes with diminution or complete loss of all sensory modalities. The cutaneous abdominal reflexes were present in all of them.

In extremely fat or relaxed abdominal walls consequent upon overdistention from pregnancy, intra-abdominal tumors, or ascites, the cutaneous abdominal reflexes are often absent. However, Walshe[58] obtained the superficial abdominal reflexes in the majority of normal people, even when the abdominal wall was obese. Rolleston,[52] studying the absence of the reflex in typhoid fever, stated that under the age of 50, in spite of a fat and wrinkled abdominal wall, the abdominal reflexes could be obtained in nearly all cases. Baldi[59] concluded that after the third pregnancy he could not find even a suggestion of the reflex. He explained his results as due to scars in the abdominal wall, the striae gravidae, which caused differences in the sensitivity of the abdominal wall. In table 6 is shown the relationship between the cutaneous abdominal reflexes and the number of pregnancies. From this there is no clear-cut indication that numerous pregnancies result in absence of the cutaneous abdominal reflex.

In table 7 is shown the relationship between the cutaneous abdominal reflexes and obesity (weights over 200 pounds) and flabby abdominal walls. The reflex was absent in only 20.2 per cent of these cases.

From table 8 it is noted that, in abdominal distention by ascites and intraabdominal tumors, the cutaneous abdominal reflexes were absent in less than half of the cases.

Pronin[60] studied the relationship between recent and old abdominal wall scars and the superficial abdominal reflexes. His series consisted of 138 patients, 81 men and 57 women.

TABLE 5

DIAGNOSES OF CASES WITH ABSENT CUTANEOUS ABDOMINAL REFLEXES

Diagnoses	*Cases With Other Nervous System Lesions*	*Cases Without Other Nervous System Lesions*
Cardiovascular disease:		
Rheumatic	2	15
Arteriosclerotic	12	40
Hypertensive	14	34
Luetic	1	2
Coronary thrombosis	2	5
Pulmonary diseases:		
Lobar and bronchopneumonia	2	19
Bronchitis	1	10
Tuberculosis		3
Asthma		13
Carcinoma		5
Bronchiectasis		2
Gastrointestinal disorders:		
Carcinoma	13	18
Cholecystitis and cholelithiasis	5	17
Gastroenteritis	2	3
Appendicitis	1	4
Cirrhosis of liver	2	3
Hernia	2	2
Peptic ulcer	2	2
Hemorrhoids	1	3
Gynecologic disorders:		
Pelvic infections	4	20
Fibroid tumors	3	15
Malignant tumors	3	6
Incomplete abortion	3	23
Blood dyscrasias	2	4
Hyperthyroidism	1	8
Diabetes mellitus	3	15
Cataract	1	
Rectal stricture	1	
Insulin shock	1	
Breast abscess	1	
Intestinal obstruction	1	
Osteoarthritis	1	
Miscellaneous: Nephritis, breast cancer, cataract, arthritis, allergy, etc.		35

TABLE 4

ASSOCIATION OF ABSENCE OF CUTANEOUS ABDOMINAL REFLEXES WITH OTHER EVIDENCE OF NERVOUS SYSTEM DISEASE IN 2,500 HOSPITAL CASES

Age Groups:	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80+
Number of absent abdominals	0	3	6	9	13	19	22	14	1
Total number of cases in this age group	89	368	534	474	388	318	230	90	9
Per cent of absent abdominals	0	0.9	1.1	1.9	3.3	5.9	9.6	15.5	11.1

TABLE 6

RELATIONSHIP BETWEEN CUTANEOUS ABDOMINAL REFLEXES AND NUMBER OF PREGNANCIES

Pregnancies:	0	1–3	4–6	7–9	10–12	13–15	16+
Abdominals present	223	529	156	41	9	5	3
Abdominals absent	33	108	59	17	10	6	
Per cent abdominals absent	12.8	18.9	27.4	29.3	52.5	45.5	

TABLE 7

RELATIONSHIP BETWEEN CUTANEOUS ABDOMINAL REFLEXES AND OBESITY AND FLABBY ABDOMINAL WALLS

Abdominals present	171
Abdominals absent	56
Per cent abdominals absent	20.2%

TABLE 8

INCIDENCE OF CUTANEOUS ABDOMINAL REFLEXES WITH ANASARCA AND DISTENDED ABDOMENS

Number with abdominals	20
Number with absent abdominals	17
Per cent absent abdominals	45.9%

TABLE 9

SINGLE ABDOMINAL WALL SCARS AND THE CUTANEOUS ABDOMINAL REFLEXES

Site of Abdominal Wall Scar	*Total Number of Cases*	*Absence of Cutaneous Abdominal Reflexes in—* *Right Upper*	*Right Lower*	*Right Side*	*Both Lowers*	*All*	*Pct. of Absence of Cutaneous Abdominal Reflexes*
Right upper	38	1	1	1		7	26.3
Right lower	129			1	4	18	17.8
Left upper	4						0.0
Left lower	19					1	5.3
Upper midline	17					5	29.4
Lower midline	108				4	17	19.4

In recent cases of appendectomy and herniorrhaphy one to three weeks after operation, the cutaneous abdominal reflex was absent in 66 to 70 per cent on the side of the operation. However, in older patients, from several months to years after operation, they were absent in 35 per cent of the appendectomies and were not absent in any of the hernia cases. In table 9 is shown the relationship between single abdominal wall scars and the cutaneous abdominal reflex; the results show that the right upper cutaneous abdominal reflex was more often absent after liver, gallbladder, and stomach surgery than the right lower cutaneous abdominal reflex following appendectomy. As indicated in table 10, with multiple abdominal wall scars, the cutaneous abdominal reflexes were absent only in 30 per cent with two scars, and in 60 per cent with three scars; they were present in one patient with four scars.

Most diagnostic import is attached to diminution or absence of the cutaneous abdominal reflexes. However, hyperactivity of the superficial abdominal reflexes has been noted in several conditions and such exaggeration of the reflexes may also be of diagnostic value. The present invesitgator confirms the finding of hyperactivity of the cutaneous abdominal reflexes fairly frequently in patients with chorea and paralysis agitans,[24] in patients with parkinsonism following epidemic encephalitis,[61] and in patients with tabes dorsalis.[1,62,63]

TABLE 10

INCIDENCE OF CUTANEOUS ABDOMINAL REFLEXES WITH MULTIPLE ABDOMINAL WALL SCARS

Number of Scars:	*Two*	*Three*	*Four*
Abdominals present	27	5	1
Abdominals absent	11	3	
Per cent abdominals absent	40.8	60.0	

SUMMARY AND CONCLUSIONS

1. The cutaneous abdominal reflexes were investigated in two groups of people. Group 1 was composed of 2,500 non-neurologic admissions to a general hospital; group 2 was composed of 1,000 psychoneurotic patients.

2. The cutaneous abdominal reflexes were absent in 16.5 per cent and 8.4 per cent of groups 1 and 2, respectively.

3. There was a higher incidence of absence of the cutaneous abdominal reflex with age.

4. The cutaneous abdominal reflexes were absent in females more often than in males—17.8 to 13.8 per cent and 9.5 to 6.6 per cent in groups 1 and 2, respectively.

5. Other evidence of neurologic involvement was present in only 21 per cent of the cases that had absent cutaneous abdominal reflexes.

6. Pregnancies, abdominal wall scars, obesity, and distended abdomens did not result in a great loss of the reflexes.

7. Absence of the cutaneous abdominal reflex in itself is not an indication of nervous system disease.

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Face-Hand Test and Background Activity

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BENDER AND HIS ASSOCIATES have conducted a series of studies on disorders in perception since 1943. These studies showed the method of double simultaneous stimulation to be unique in revealing disorders such as the phenomena of extinction (the perception of only one of two stimuli applied to different areas of the sensory field) and displacement (the mislocation of one stimulus in a predictable direction.)[1]

In 1949 Bender, Shapiro, and Schappell,[2] working with hemiplegic patients, found that the most effective method for eliciting the phenomenon of extinction was simultaneous stimulation of the face on the healthy side and the hand on the hemiplegic side. With this technic, the stimulus to the hand is most commonly extinguished and that to the face is almost always perceived. This pattern is known as face dominance.[2] Later Bender, Fink, and Green[3] described the patterns of perception upon simultaneous stimulation of the face and hand in patients with aphasia, organic mental syndrome, and schizophrenia, as well as in normal adults and children. Face dominance was the rule in all of these subjects. Face dominance was most conspicuous and persistently present in patients with organic mental syndrome, in the very aged, and in very young people. They concluded that a positive face-hand test (that is, extinction of the hand or displacement from hand to face on double simultaneous stimulation of these two areas) formed a consistent part of the organic mental syndrome or organic psychosis in any patient between the ages of ten and 65 years.[4] Finally, in 1954, these authors determined the general pattern of perceptual organization, with simultaneous stimuli testing various combinations of two parts of the organism. Here again the face was the most dominant region. The genital zone was next in the order of dominance, while other parts followed in a gradient with the hand showing the least dominance.[5]

The persistence of this pattern poses several questions, some of which are: 1) does the organism merely respond to the stimulus having the most significance in its total activity?[6] 2) can the pattern of face dominance be explained as a type of extinction or displacement to inattention?[7,8] and 3) can the order of dominance be changed by directing more attention to a zone of least dominance, such as the hand?

This study was designed in an attempt to answer these questions. Specifically it was asked whether changing the relative position of the hands or using the hands during double simultaneous stimulation would affect the pattern of face dominance.

SUBJECTS AND METHODS

The face-hand test was given to 500 patients admitted consecutively to the psychiatric division of Bellevue Hospital before any other examination was performed. No history was taken and the only questions asked were the name and age. The subjects consisted of 256 females and 244 males.

Each patient was tested under two conditions: 1) in a sitting position with the eyes closed and the hands resting on the knees, and 2) walking with the eyes closed, the upper extremities extended forward, so that the hands or fingertips will serve as feelers. In some cases when the patient was unable to sit, the hands were placed on the chest for condition 1, and the arms extended upward for condition 2. When the subject could not walk, condition 2 was fulfilled by extending the arms forward. The subjects were given ten trials under one condition and ten trials under the other condition. Half the patients were first tested under condition 1, the other half were first examined under condition 2. Each trial consisted of touching simultaneously and equally the cheek and dorsum of the contra- or ipsilateral hand. At times in condition 2, the hands were also touched on the tips of the fingers. The patients were asked to report where they were touched. In the instances when only one percept was reported, the subject was asked whether he was touched anywhere else. The face-hand test was considered positive when only one percept was reported in the first five trials.

All subsequent clinical and laboratory examinations were conducted on the ward. The clinical diagnoses with which the results were compared were made by a senior psychiatrist. In approximately one-fifth of the cases there was also a complete neurologic study.

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TABLE 1
RESPONSES OF 500 PSYCHIATRIC PATIENTS TO THE FACE-HAND TEST

	Face-hand Test Positive	Negative	No. of Cases	Positive Results
Organic group	190	40	230	83%
Non-organic group	40	230	270	15%

RESULTS

Classifying results in terms of "organic"* and "non-organic," the final ward diagnosis of the 500 patients examined in the psychiatric admitting office was 230 organic and 270 non-organic. Of the 230 organic patients, 190 (83 per cent) had a positive face-hand test and 40 (17 per cent) a negative test. Of the 270 non-organic patients, only 40 (15 per cent) had a positive test and 230 (85 per cent) a negative test. Thus, 83 per cent of the organic group gave a positive response and 85 per cent of the non-organic group a negative response (table 1).

Of the organic patients, a total of 174 were tested under the two experimental conditions; of these, 130 gave a positive response in both conditions and 33 a negative response in both. It follows that identical results were obtained in 163 cases, which represents 94 per cent. Only 11 cases showed a discrepancy. In nine patients the test was positive in condition 1 and negative in condition 2; in two patients it was just the opposite (table 2).

In the non-organic group, 256 cases were tested under both conditions. Of these cases, 26 gave a positive response in conditions 1 and 2 and 221 had a negative response. Thus, identical responses were obtained in 247 non-organic patients, which represents 96 per cent similarity between the two conditions. In only nine cases the results were dissimilar; in six cases it was positive in condition 1 and negative in condition 2; in three cases it was just the opposite (table 3).

The variant of condition 2, in which the tips of the fingers were touched instead of the dorsum of the hands, was given to 42 patients. This change did not alter the general result.

*By organic we mean the manifestation of at least three of the following symptoms: impairment in orientation, memory, calculation, or general information; rigidity and concreteness of thinking; and inability to handle more than one situation at a time.

TABLE 2
RESPONSES IN 174 CASES OF ORGANIC PSYCHOSIS UNDER BOTH EXPERIMENTAL CONDITIONS

Condition 1	Condition 2	No. of Cases
+	+	130
—	—	33
	Total identical responses:	163(94%)
+	—	9
—	+	2
	Total different responses:	11 (6%)

TABLE 3
RESPONSES IN 256 CASES OF NON-ORGANIC PSYCHOSIS UNDER BOTH EXPERIMENTAL CONDITIONS

Condition 1	Condition 2	No. of Cases
+	+	26
—	—	221
	Total identical responses:	247(96%)
+	—	6
—	+	3
	Total different responses:	9 (4%)

DISCUSSION

This study most clearly answered the question of the effect of purposeful activity or attention upon the pattern of face dominance. Goldstein[6] maintained that the meaning of a stimulus can be understood best in terms of the total activity of the organism at the time. He postulated that, if two stimuli are applied simultaneously and represent two unrelated performances which the organism is not able to fulfill at the same time, only one will be effective. Moreover, the effective response will be the one which is more important for the total organism, and in test condition 2 it should be the hand which should be more responsive.

The data obtained in our experiments do not support such a theory. It is evident that in any subject, when walking with the eyes closed and the arms and hands extended forward, the tips of the fingers should represent the vanguard against his environment. The subject is directing his attention to the hands more than to other parts of the body. The extended hands, therefore, would appear to play a more important role than the cheek in the relationship between the total organism and its surroundings in test condition 2. According to Goldstein's theory, one would expect that under condition 2, of the stimuli applied simultaneously to the fingertip and the cheek, there should be a dominance of the hand over the face. Our results, however, indicated no such dominance. In fact, the face remained dominant over the hand, even when the subject used his hands for protection.

Our results fit in with the findings of Bender and co-workers who showed that there is no difference in the pattern of responses among subjects affected with congenital blindness or blindness acquired in early childhood.[5] In these subjects, too, the hands and fingers are of special importance. The blind under the age of six and the blind adult with mental deficiency or organic mental syndrome like the non-blind also show a high incidence of face dominance.

The observations of the present study demonstrate the inadequacy of the explanation of the phenomenon of extinction in terms of altered attention, as advocated by Critchley.[7] In condition 2 the patients were tested near the wall of the room. Sometimes, while being tested, they hesitated to walk farther because of the risk of bumping against the wall, using the fingertips as guides. In this situation the fingertips became one of the principal organs of perception and were presumably a focal point for self-protection. Nevertheless, the pattern of face dominance was not altered.

The persistence of this pattern was also observed in many of the non-organic patients who failed in the first two or three trials. It must be assumed that the physiologic components of attention, in the sense of Reinhold,[8] were intact in this group. From our eclectic point of view, attention, as any other psychic phenomenon, has a physical substrate from which it cannot be separated. This physical substrate apparently is not damaged in the non-organic patients. Inattention might play a role in the extinction effects found on the contralateral side of a patient with a parietal lobe lesion, but inattention does not serve as a general explanation for the pattern of dominance, as described by Bender, Green, and Fink.[5] It would seem highly improbable that the subject was consistently inattentive only in certain areas (hands).

Our results confirm the observations of Bender and associates in 1952.[4] They found a positive face-hand test in 87 per cent of 156 patients with organic mental syndromes tested with or without previous knowledge of the patient's mental status. We found 83 per cent with a positive face-hand test among 230 patients in whom the examination revealed an organic psychosis. We differ slightly, however, as far as the non-organic group is concerned. In this type of patient they found only 3 per cent to have a positive face-hand test. Our figures indicate 15 per cent. This difference is probably due to the different criterion of positivity used. We scored the responses to the first five trials instead of ten trials. With our criterion their percentage rises to 11 per cent. It should be stressed that this change in criteria did not alter the general results in the organic group. We may also mention that most of our organic patients who responded correctly to the test were among the group of acute syndromes, especially those with alcoholic intoxication. Only 78 per cent of positive cases were found in this group. It is possible that many of them were admitted with an intoxication of a mild degree. On the other hand, this percentage rose to 91 per cent among senile and arteriosclerotic patients.

In conclusion, the significance of this study is to affirm that face dominance over the hand does not depend on the relative position in space of the areas tested, nor upon the function they were performing at the time of the examination, nor upon the factor of attention. This pattern of dominance, which seems to be related to an inherent sensory organization, becomes more apparent in diffuse brain disease.

SUMMARY

1. Five hundred psychiatric patients were given the face-hand test in the admitting room under two conditions: 1) standard and 2) walking with the eyes closed while the arms were extended forward. The results were then compared with the final clinical diagnosis and correlated with the final mental status determined after a period of observation.

2. It was found that the response to the face-hand test does not depend on the relative position in space of the body parts tested, nor on the function these parts were performing at the time of the examination, nor upon the factor of attention.

3. Previous studies as to the value of the face-hand test in the diagnosis of organic psychosis are confirmed.

4. The results are discussed in terms of current theories of perception of simultaneous stimuli.

The authors wish to express their gratitude to Dr. Morris B. Bender for his help and advice in this study.

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New Dimensions in Electroencephalography

Reginald C. Bickford, M.D.

SOME EIGHT YEARS AGO, Jasper,[1] in a classic discourse on charting the sea of brain waves, implied a two-dimensional approach to the problem. I believe we can now add two more important dimensions: the third dimension of brain recording, now usually termed "depth electrography," and the reverse process, that of introducing a stimulus pulse into a part of the brain and recording its electrical echoes and local electrical and clinical effects, a procedure which could be called "electrostimography." These two developments have come at a time when the field of electroencephalography was showing signs of having reached the limits of advance, using presently available methods. Many workers have felt that the major defect of our science was in reality a very simple one, namely, that we were trying to unravel the complex problems of cerebral function when only about 1 per cent or less of the brain mechanism was open to our inspection. I refer, of course, to the very limited access to the electrical activity of the whole brain or even of its convoluted surface that conventional scalp recording provides. This coverage has not been significantly increased by the subtle and daring attempts that have been made to gain closer access to the brain by introducing electrodes into various cranial foramina.

Over the years, our exclusion, as electroencephalographers, from essential components of the brain mechanism has been emphasized by the unveiling of important subcortical and intracerebral mechanisms by neurophysiologists in the animal field. Such work has been that of Hess[2] on diencephalic mechanisms, that of Magoun[3] dealing with coma mechanisms, Li and Jasper's[4] recent demonstration that electrical discharges, even 1 mm. or so below the cortical surface, may be quite different from those recorded from a surface lead, and also the work of numerous investigators on limbic structures. An end to this period of frustration now appears to be in sight. The methods of human depth electrography developed or at least perfected over the last five or ten years now provide us with an adequate method for access to most areas of the human brain. My present task is to assess the magnitude of this advance and to determine whether in fact it is likely to provide the answers to the many questions that plague us as electroencephalographers. It will be unnecessary to detail the work that has been done in this field. Reference will be made only to methods employing implanted leads, since operating room probing technics, though useful for certain purposes, are strictly limited in their application. These limitations include the patient's reaction and the electroencephalographic effects caused by discomfort, sedation, or anesthesia, in addition to the restrictions of recording time and instrumentation. Methods of chronic implantation in the human have been developed by a number of workers including Spiegel and Wycis,[5] Delgado, Hamlin, and Chapman,[6] Heath and co-workers,[7] Jung in Germany,[8] Brazier,[9] Kellaway,[10] and others. Our own technic of implanting fine multicontact leads was first developed in England in 1943 and, so to speak, was reactivated by the interest of Dodge at the Mayo Clinic and Petersen and Sem-Jacobsen at the Rochester State Hospital. At this time, the findings in a group of 31 patients treated at the Mayo Clinic will be reviewed. These were all epileptic patients with seizures uncontrolled by adequate medication and in whom there was suggestive clinical or electroencephalographic evidence of a focal origin for their seizures. To review this material in any detail would obviously take much longer than my allotted time, and I intend merely to highlight findings from our own experience which seem significant and which may indicate trends for future development.

TECHNIC

We now use 40-gauge stainless steel wires, since Fischer and associates[11] have shown that both copper and silver are toxic to the brain and cause sterile abscesses to form. As many as 12 such wires can be stranded together, the tip of each wire being bared for 1 mm. and usually separated from its neighbors by 0.5 to 1 cm. A commonly employed electrode has eight such contacts separated by 1 cm. The

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Presidential Address at the meeting of the American Electroencephalographic Society, Atlantic City, New Jersey, June 15 to 17, 1956.

leads are introduced into the brain by means of a fine (21-gauge) stilet inserted through a burr hole placed in the appropriate cortical area. While such leads can be placed stereotactically, they are more usually introduced by hand and directed so as to cover a certain region in which, for instance, clinical and electroencephalographic evidence may have indicated the probable existence of a scar. The position of the leads is subsequently ascertained roentgenographically, and we have been greatly assisted by maps showing location of internal brain structures on roentgenograms. We do not believe, however, that stereotactic maps prepared on normal material will give any satisfactory answer to the anatomic localization of electrodes in many of the epileptic cases, for the following reasons: In the first place, these cases often show considerable distortion of the brain due to scarring and atrophy, in addition to possible developmental anomalies, such as smallness of one hemisphere; secondly, we are not in general aiming at placing electrodes in specific structures, but trying to locate the position of discharging foci of unknown distribution. A recent modification of our established technic allows recordings to be made at the time of introduction of the electrode, thereby combining some of the advantages of the acute brain probing and simultaneous recording with those of the implanted electrode technic.

There will naturally be interest in the safety of the technic. In the Mayo Clinic group of cases (31 in number) no serious complications have developed which could be attributed to the technic. The risk, therefore, is that of placing burr holes with the patient under general anesthesia, there being no particular hazard from passing through such structures as the pyramidal system or the visual fibers; at least, the effects have been so minimal that they cannot be detected by presently available tests. Likewise, the risk of hemorrhage or infection seems to be minimal so long as proper precautions are taken, such as limiting investigations to cases without gross arteriosclerosis and without vascular anomalies. With the routine use of antibiotics during the period of implantation, there have been no infective complications.

Other points concerning the technic are illustrated in figure 1. It will be noted that a special switch has to be used, the Gilson model, since as many as 100 intracerebral contacts may result from implantation of the leads. In addition to intracerebral contacts, scalp contact is made by small stainless steel skin

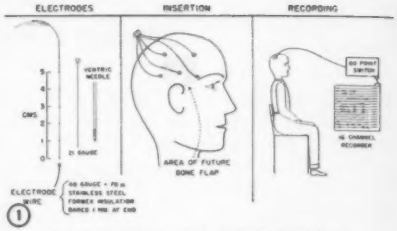

FIG. 1. Diagram of over-all depth technic.

sutures consisting of 40-gauge wire bared at the suture area. Connections are made from a socket stored in the head bandage. When the electrodes have been implanted, recordings are made in the electroencephalographic laboratory. The patient is ambulatory and free from discomfort. It has been common practice to record the electroencephalograms of patients for periods of four to 14 days, during which time detailed observations can be made with such activating technics used as sleep, pentylenetetrazol (Metrazol), and electrical stimulation effects. The electrodes are finally removed by gentle traction, no anesthesia being necessary.

A depth electroencephalogram, or "electrogram," as it is now more usually called, looks on superficial examination much like the conventional scalp recording. The alpha rhythms and beta rhythms are seen, the former often showing good inhibition with eye opening; if the patient is an epileptic, one may notice spike foci, synchronous or independent in different channels. Furthermore, if the patient has attacks of petit mal, one is likely to see spike-and-wave discharges in the depth that are indistinguishable from those recorded from inline electrodes across the scalp. However, the absence of eye blink and muscle artifact and the flattening of electrical activity from contacts situated in the ventricle are characteristic of the depth electrogram. Those observing depth records for the first time are likely to be surprised, because there appears to be no clear distinction between what they assume to be cortex in the upper contacts and white matter in the depth. A few moments of observation of a series of brain slices might quickly dispel this oversimplified conception. In fact, there is practically no approach which can be made through depths of the human brain which does not offer a high probability of encountering mixed layers of cortical gray and white matter to a depth of at least 4 cm., such is the extreme convolution of the brain in all areas, in

addition to the deeply convoluted structures such as the Sylvian fissure, the rolandic fissure, the insula, and the calcarine fissure. This, however, is not the only reason for the apparent lack of discreteness in many of the rhythms of the depth electrogram. This results at least partially from the circumstances of diffuse generation of the rhythms. On the other hand, many sharply localized discharges may be encountered in the depth electrogram. A good example of this is the fast activity that may be recorded from a depth lead, one contact of which was in the olfactory bulb.[12] This draws attention to a finding which is seen repeatedly in the depth, that of fast rhythmic discharge to an afferent stimulus, a new phenomenon in electroencephalography and probably of significance in our interpretation of central sensory mechanisms. The existence of these fast response mechanisms has been noted by Sem-Jacobsen and associates.[13] In figure 2 is an interesting example encountered in a recent patient. Note the very fast rhythmic discharge associated with illumination of the eyes. This response could be demonstrated equally well during sleep. Its frequency ranges from 30 to 60 cycles per second.

Unfortunately, we cannot spend more time on the subject of normal depth rhythms, but I hope that enough has been said to indicate some differences from more conventional recordings. It is possible that, with more sensitive frequency analysis tuned to the appropriate frequency range, we may be able to detect some of these fast rhythms described in the depth by conventional recording. An important function of the fast rhythms in the future will undoubtedly be their use as physiologic localizers providing information concerning contact location.

Let us now pass to highlight the findings in epileptic patients, which have been the main subject of our endeavors. In the first place, a preliminary survey indicates that initially depth

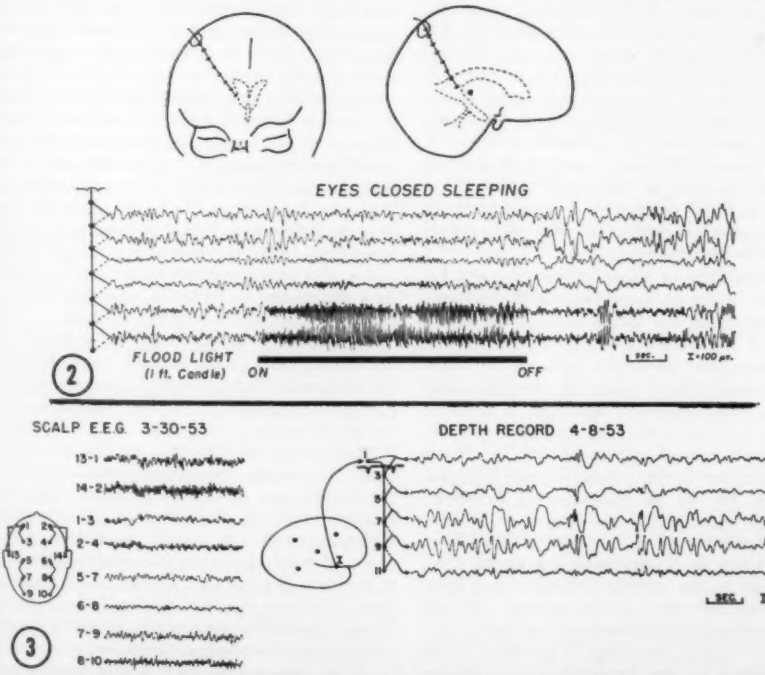

FIG. 2. Fast discharge evoked in the depth contacts of an electrode in the anterior calcarine area in response to illumination in a sleeping patient. Ventricular outlines are dotted.

FIG. 3. Spike discharges occurring in depth (contact 7) which rarely penetrate to more superficial contacts near the cortical surface. The conventional recording on this patient, illustrated on left, showed only some minimal focal fast activity in the right Sylvian region and no spike discharges. Spike discharges had, however, been recorded several years previously in the same region.

electrography is not going to simplify the epileptic problem. Almost without exception, scar foci, for instance, appear much more complex in depth when compared with the conventional electroencephalogram. Of course, it is not very surprising on statistical grounds that the depth, which contains perhaps 90 per cent of the spike-producing gray matter, should reveal many discharges not observed on the surface. Another important consideration is, however, the fact that important structures such as the uncus and amygdala, suspected of being involved in temporal lobe seizure mechanisms, are relatively inaccessible to conventional surface recording, except by way of projected disturbances. We have repeatedly observed the occurrence of seizure discharges in the depth of a temporal lobe which show little indication of their presence in the surface leads or even in the more superficial contacts of the depth lead, as is indicated in figure 3. This inaccessibility of the discharging lesion doubtless accounts for some of the negative or inconclusive conventional electroencephalographic findings of patients suspected on clinical grounds of having temporal lobe seizures. It is obvious that, if these foci are to be eradicated surgically, their localization in depth is a necessary preliminary to accurate excision. I have not time to discuss a number of difficult questions that arise in this connection, such as whether a focal discharge is primary or is being triggered as part of a more widespread synchronized discharge.

The possibility of using depth contacts for stimulation gives us important additional evidence concerning the localization of the initial features of the patient's seizure. In a routine depth procedure, all depth contacts are stimulated systematically and, if the electrode array has been properly oriented, it is usual to find a contact whose stimulation produces the same sequential appearance of symptoms as that manifest in the patient's usual epileptic attack. It has to be remembered, however, that depth stimulation of tracts may produce a seizure discharge at a distance; therefore, such evidence as is obtained from depth stimulation has to be viewed critically and integrated with our other electrographic, clinical, and roentgenographic evidence of local disturbance. Used in this way, it provides a valuable technic in the localization of a lesion before operation. There are, however, additional functions, for stimulation carried out on the periphery of a lesion also gives valuable information as to other functional structures in the vicinity of the lesion which, in itself, has a considerable bearing on the feasibility of excision.

Let us turn to discuss the findings by depth recording in psychotic patients. These have been a subject of controversy for obvious reasons. In the first place, no workers in the field have unequivocal normal material for the establishment of norms for the frequency of depth rhythms, and there has been a tendency to assume that the frequency characteristics of the depth rhythms might show the same range as those established for surface recordings. This is already known to be untrue for some of the faster rhythms recently discovered in the depth. A second criticism properly directed at this work is that the spike discharge reported by some workers could occur as a consequence of neuronal damage associated with the insertion and continued presence of a foreign body in the brain. Continued experience with the method, however, tends to indicate that such factors play a minor role. For instance, electrodes placed well outside the suspected scar focus or in the opposite hemisphere rarely exhibit discharges of a kind usually discovered within the scarred area. More recently, our laboratory has carried out an extensive series of depth implantations in animals under conditions comparable to those with the human material, and has failed to record spike foci from any location in the brain. It can, therefore, be safely assumed that damage is not an important factor in producing depth spikes, and it also seems unlikely that spike foci of the kind illustrated in figure 3 represent the normal discharge of any depth structure.

The findings in psychotic patients, as described by Sem-Jacobsen and co-workers[14] in the Rochester State Hospital, indicate that the paroxysmal discharges in the two to five per second frequency range are noted frequently in this group of patients. In the absence of norms for depth, little significance can at present be attached to this observation. However, a more challenging finding of these workers is the occurrence, in a small proportion of their cases, of marked seizure-like discharges related to active hallucination. Rather similar findings have also been reported by the Tulane group.[7] These reports are particularly interesting, since hallucinatory processes might be expected to be those that would form a link between the epileptic and the psychotic syndrome, if any such relationship does, in fact, exist. Before we can accept these findings, however, some critical evaluation is needed, since it has to

be remembered that an excited hallucinating patient is in an abnormal physiologic state. It is possible, therefore, that at least some of the changes reported could be regarded as secondary to some of the following events: 1) hyperventilation, almost inevitably associated with agitation and a potent initiator of paroxysmal slow-wave activity in the depth electrogram; 2) electrical discharges, associated with proprioceptive bombardment induced by the movement ordinarily accompanying an agitated hallucinated condition; 3) visual activity, producing lambda waves and fast activity in the posterior head recordings; and 4) movement artifact and vascular pulsation, which may appear in depth recordings under these circumstances. While these factors do not seem to have been adequately controlled in the researches published so far, there does, nevertheless, appear to be acceptable evidence for the existence of a group of patients classified as psychotic who exhibit electrical changes suggestive of a relationship to the epilepsies or at least sharing a common hallucinatory mechanism. This question is worthy of more consideration as presently one of the most important contributions of depth electrography to the elucidation of psychotic mechanisms.

Now let us turn to consider an exciting new field for electroencephalographers, that of electrostimography. This field results, of course, from our ability to use depth contacts for introducing stimuli at selected points and employing other intracranial and surface contacts to intercept the transmitted disturbance so induced. Stimulation of the brain via afferent pathways with simultaneous observation of the electrical disturbance induced is, of course, a well-established technic in neurophysiology. With depth stimography we have a technic in which a known amount of stimulation can be applied to regions of the brain inaccessible to afferent volleys and unlimited by the properties of receptor and transmission mechanism. Observations concerned with faster rates of stimulation (20 to 100 per second) have already been mentioned as an important part of the investigation of epileptic patients with the use of implanted leads. The detailed study which can be given to the patient's symptoms, evoked by stimulation, gives the method a considerable advantage over operating room technic, though in general the results and interpretations parallel the classic observations of Penfield and Jasper[15] on accessible regions of the cortex. Depth stimography, of course, allows the investigation of hitherto inaccessible regions of the brain. I should have liked to show the motion picture of an eight year old boy in whom depth stimulation in the superior temporal gyrus gave rise to auditory hallucinations of people shouting to him across the street, asking him to come and play. It illustrates very well how specific experiences related to stimulation may be, and how exactly they may reproduce the patient's aura. The degree to which the induced pattern and the "natural" seizure pattern correspond naturally influences the confidence with which the finding can be interpreted as indicating the true locus of origin of the patient's seizures.

While fast stimulation is most effective in evoking epileptic discharges and is therefore a most useful screening technic for locating the origin of a patient's seizure discharge, we have recently found that slow-pulse stimulation technics provide important information of another kind. Such single 0.3 millisecond pulses repeated at intervals of 0.5 to 3 per second may produce behavioral changes in the patient and yet show little tendency to initiate self-sustained epileptic seizures. In addition, technics have now been evolved which allow a simultaneous recording from most of the intracerebral contacts during slow stimulation. This

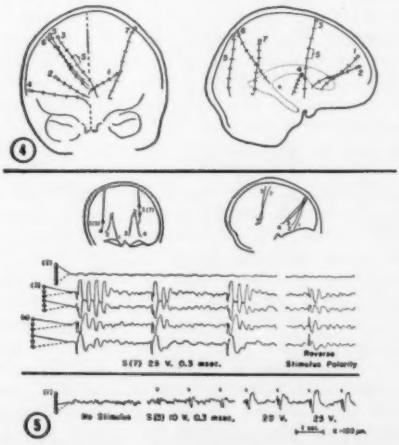

FIG. 4. Contacts stimulated (S) on electrode 3 to produce repetitive movement. None of the other contacts produced this effect on stimulation. Ventricular outline superimposed from earlier air encephalogram is shown dotted. Superimposition was not possible in the anteroposterior view.

FIG. 5. Distant rhythmic responses evoked by single-pulse stimulation. Stimulus artifact is seen initiating each train of high-voltage waves. Stimulus points (S) are marked on electrodes 7 and 5 in the head diagram.

has revealed the existence of remarkable transmission mechanisms in all parts of the brain.

Let us first take an example of the behavioral effects that may follow slow stimulation. For this purpose, I am going to show a sound motion picture of a patient recently investigated with focal right cerebral epileptic attacks. In such investigations we normally implant electrodes on the periphery as well as in the center of the suspected scar lesion. In this particular patient, stimulation of contacts of a lead passing through the right premotor regions, as shown in figure 4, produced a remarkable effect. Shortly after commencing stimulation on these contacts with a parameter of 10 volts, 3 per second pulses of 0.3 millisecond and 2 milliamperes peak current, the patient would commence a variety of repetitive movements, sometimes of quite complex character and involving one or both hands or feet or a combination of limbs. The movement would persist indefinitely so long as the stimulus was continued (up to 20 minutes). As will be seen in the motion picture, the patient, though ordinarily quite cooperative, would not stop the movement on demand. However, consciousness was maintained and, though conversation was never much more than a nod or a monosyllable during stimulation, she was able to recall complex numbers that she was told to remember during stimulation. An awkward catatonic posture was often adopted by the patient while indulging in the complex repetitive movements, this disappearing immediately on cessation of the stimulus. On one occasion, the patient was awakened from sleep by the occurrence of a repetitive movement induced by stimulation. The movements exhibited a great variety of forms but were always appropriate to the particular environmental situation and were modified by its changes (objects handled). It should also be noted that the phenomenon could not be induced by similar stimulation of other contacts. The movements induced did not seem to be related to the patient's personality, insofar as she did not manifest such ticlike movements normally, nor were they related to her epileptic attacks, which were characterized by sudden loss of consciousness with head turning to the left. The threshold voltages for the onset of the movement remained constant over several days. [At this point in the address the motion picture previously referred to was shown.]

And now for the questions I am sure you are asking. First, what is the location of the contacts, and second, what is the significance of these findings? Location of the depth contacts by roentgenographic technic places them just lateral to and above the medial part of the lateral ventricle, probably in the callosal fibers and within 0.5 cm. of the body of the caudate nucleus. We have seen that stimulation of this region gives rise to repetitive movement, the particular form of which is largely dependent on environmental circumstance. This finding, together with the absence of any constant involvement of contralateral limbs and the loose relationship between stimulus frequency and individual movement, all indicate a mechanism of a higher order of integration than has hitherto been discovered in the motor cortex. The pronounced repetitive nature of the movements, which resembled common tics, suggests that a neurologic mechanism has been revealed which could underlie many of the compulsive movement symptoms that are seen in normal persons and in clinical syndromes. The limitation of communication, the awkward catatonic posture, and the suspicious attitude of a patient developed during stimulation are also of interest insofar as their possible relationship to schizophrenic syndromes is concerned. Indeed, more investigation of this general region in both animal and human is indicated by our results, which have revealed an unsuspected complexity of function associated with the stimulated zone.

I should not like to close this account of depth stimulation without making reference to some remarkable transmission effects following single-pulse stimulation of the kind whose behavioral effects we have just discussed. The electrical effects of such stimulation may be summarized as follows: 1) Many different kinds of response pattern have been evoked at a distance from the stimulation locus by single-pulse stimulation. The evoked responses include spikes, sharp waves, spike-and-wave patterns (figure 5), and rhythmic repetitive waves of frequency ranging from 2 to 20 cycles per second and of amplitudes up to 1,000 microvolts. 2) Relationship to background: In some instances it is clear that background activity present spontaneously is being triggered. Examples have been investigated of the triggering of wicket rhythm in the motor area of spindles during sleep and of spike discharges resembling 14-and-6 waves. In most instances, however, the responses arise from a relatively flat and featureless background. 3) In a general way, depth contacts can be classified as transmitter or receiver areas, though the precise significance of this finding has yet to be

elucidated. Rhythmic trains of waves lasting up to three seconds have resulted from single-pulse stimulation, and it is remarkable that these large discharges frequently seem to have no detectable clinical accompaniment, though, as we have seen, there may be very subtle behavioral changes. While commonly no clinical change can be detected, a number of patients have manifested perseveration in speech and motor activities such as drawing. Many observations have been made of transmission effects during sleep and in anesthesia, and most of these findings indicate that transmission pathways are open during sleep, though there may be some modification in the rhythmicity of the evoked response. During anesthesia, there is a definite reduction in transmission, the response being reduced in amplitude, duration, and complexity.

Up to the present, electrostimography has provided us with a bewildering complexity of information, since it appears that most signal inputs to the brain are widely transmitted to other areas. This might have been anticipated, since transmission of information is a primary function of the brain. When patterns of transmission are better understood, the technic should provide much needed information concerning localization of intracerebral contacts. The findings already outlined indicate that the method should be valuable in quantitation of the effects of drugs on intracerebral transmission. For instance, an investigation of the effect of tranquilizing drugs on this transmission would be of considerable interest.

Finally, a word concerning some general implications of these technical advances. The coming of new dimensions in our science cannot fail to broaden the outlook of the electroencephalographer. No longer will he be limited by the complexities of recorded electrical events at the surface of the head, since he will have direct access to both the electrical and the behavioral mechanisms within the depths of the brain. Thus, he will be in a position to contribute in a more significant way both to the problems of clinical diagnosis and to the common goal of understanding brain function.

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Refsum's Syndrome

An Unusual Hereditary Neuropathy

Ross Fleming, M.D.

In 1945 Sigvald Refsum[1] described an interesting hereditary neuropathy occurring in five members of two Norwegian families. He termed this syndrome "heredopathia atactica polyneuritiformis." Its essential features were an atypical retinitis pigmentosa, with night blindness and concentric constriction of the visual fields, development of a chronic polyneuritis-like picture in the limbs, progressive nerve deafness, ichthyosis, and high protein in the cerebrospinal fluid. In each case the disease appeared as a recessive hereditary characteristic, since all were born of consanguineous marriages.

Since Refsum's original description was published, several similar cases have been described.[2–6] Recently a family exhibiting this syndrome has been brought to light.

CASE HISTORIES

Patient N. C. (number 32 in pedigree). A 30 year old male was admitted to the National Hospital, Queen Square, on November 14, 1954. His complaints were disturbed vision, deafness, weakness and wasting of his arms and legs, and bowel and bladder disturbances. The patient's mother and father were first cousins and his sister is afflicted with a similar disease.

As a child he was normal until about the age of six when his appetite became poor and he began losing weight. He always seemed to have some impairment of vision and would grope for objects, especially in the dark. As he grew older it became quite obvious that he had severe night blindness. At the age of 15, he was seen by an ophthalmologist who recorded visual acuity of 6/9 in each eye and noted the presence of retinitis pigmentosa bilaterally. His vision deteriorated steadily in both eyes. Ophthalmologic examination one year ago revealed very pale disks, with degenerative changes in the maculae and peripheral retinae. His pupils would not dilate with homatropine. Bilateral lens opacities were present. At the present time he is able to recognize only gross forms and shapes.

As a child his legs were weak and unsteady. He was able to walk fairly well, but would fall frequently and could not play games. His arms were quite strong. At about age 14 his legs became much weaker and he started using a cane and then crutches. There has been little change in the amount of weakness of his legs since the age of 20. He has been unable to get around very well, even with crutches. Recently there has been some weakness and clumsiness in the arms.

His mother states that during his late teens he had very dry scaling skin. At age 25 he gradually lost hearing in both ears and total deafness has persisted. He has had increasing urinary frequency and occasional fecal incontinence.

The patient is a male of 30 years with marked generalized muscular wasting (figure 1). He is totally deaf and his vision is markedly impaired, so that communication with him is only possible by writing letters and words on the palm of his hand. He is fairly bright, alert, and cooperative, and assessment by the psychologist revealed little if any intellectual impairment. His speech is normal.

Cranial nerves.

I. He has complete bilateral anosmia.

II. The red reflex is lost in both eyes and opacities present in both lenses and vitreous suggest an old posterior uveitis. It is almost impossible to see the optic fundi. There is a high degree of myopia; visual acuity in the right eye is limited to light perception and in the left eye is 6/36. Visual fields cannot be assessed.

III, IV, and VI. The pupils are both very small and the right is irregular in outline. Both react fairly well to direct and consensual light and on convergence. Neither pupil dilates with mydriatrics. External ocular movements are full in all directions and there is no nystagmus.

V and VII. Normal. Taste is normal.

VIII. He has total perception deafness in both ears, but caloric responses are normal in both ears.

IX, X, XI, and XII. Normal.

Motor system. There is severe generalized atrophy of all muscles, greatest in the calf muscles and to a lesser extent in the forearm muscles. There is generalized decrease in muscle tone. There is generalized muscular weakness, with complete paralysis of dorsiflexion of both feet, and very marked weakness of the distal muscles in both arms and legs. There is a little spontaneous fasciculation in the forearm muscles. There is no myotonia. The muscles are irritable to direct percussion generally, except the most wasted ones. There is severe ataxia on the finger-nose test and heel-shin test bilaterally, probably due to the severe sensory deficit.

Reflexes. It is not possible to elicit any deep reflexes in the arms or legs. There is no plantar

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These cases were studied while the author was a clinical clerk at the National Hospital for Nervous Diseases. Author's present address is Toronto Western Hospital, Toronto, Canada.

FIG. 1. *Patient N.C.* Note the extreme wasting of leg muscles.

response in either foot. The abdominal reflexes are present and normal.

Gait. The patient cannot stand unsupported. He walks with crutches and swings his legs widely because of drop feet, and has to fling his legs forward from his trunk because of generalized weakness of hip and knee muscles.

Sensory system. There is mild blunting of pinprick and cotton-wool appreciation in the hands and in the legs below the knees. Position sense is severely impaired in both feet and legs, but normal in the left hand and only slightly impaired in the right hand. Vibration sense is absent in the hands, present at the elbows, and completely absent below the sixth dorsal spine. Stereognosis is good in the hands and trunk but absent in the legs.

General examination. There is no palpable enlargement of peripheral nerves. He has a severe kyphoscoliosis in the dorsal region. He has a minimal claw hand deformity bilaterally. He has a soft fluctuant swelling in the left breast, and a pair of accessory nipples at the level of the costal margin. Heart, chest, and abdomen are normal.

Laboratory investigation. Blood — Hemoglobin 17 grams, white blood count 10,000, polymorphonuclear cells 81 per cent, lymphocytes 16 per cent. Blood Wassermann negative. ESR 11 mm. per hour. *Urine* — No protein, sugar, or cells. Urinary porphyrins absent. Urinary amino acids 0.33 gm. in 12 hours. *Cerebrospinal fluid* — Pressure 120 mm. of water, protein 200 mg. per cent, cells 2 lymphocytes per cu. mm. *X-rays.* Chest and skull normal. Cervical spine normal. X-rays of knees reveal an unusual bone texture, with multiple Harris lines and normal joint spaces. *Electrocardiograph* (figure 2). The QRS interval is increased to 0.14 second, and the main deflection in leads 1 and 111 is down. The T wave is up in leads 1 and 111. This suggests delayed conduction. *Electromyograph* reveals fibrillation and denervation potentials in hand muscles and right quadriceps, suggestive of chronic lower motor neuron disease of long standing.

Patient M. P. (number 34 in pedigree). This patient, age 26, was seen in her home in November 1954. She is a sister of the first patient. In childhood her legs were always thin and weak and she used to fall frequently. Because of this she sustained fractures of both elbows, the right tibia, and right humerus at different times during childhood. Since her earliest memory she has been unable to see in the dark, though her vision was normal in the daytime. She was an average student in school. During her teens her skin was extremely dry and scaly. She noted fairly rapid progression of deafness in both ears, but this has never become complete. She gets along quite well with a hearing aid. In May 1952 her first child was born, and two months later she began to drag the right foot, fell more frequently, and the right foot became numb. Soon afterward the left foot began to drag

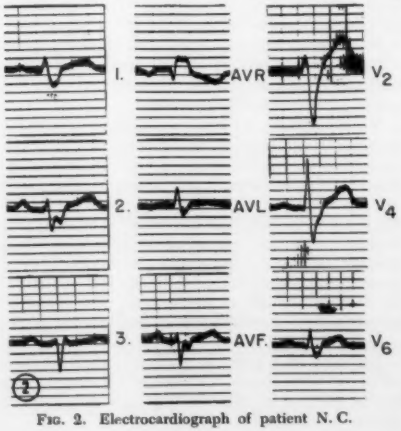

FIG. 2. Electrocardiograph of patient N. C.

and the weakness in both feet progressed. In September 1952 she was noted to have absent Achilles reflexes, a complete right foot drop, and hypalgesia over the right foot. In November 1952 she was noted to have bilateral nerve deafness but otherwise normal cranial nerves. Her arms were normal. She had bilateral foot drop, absent ankle jerks, but no sensory loss. X-rays of the skull, spine, and chest were normal. A myelogram was normal. An intravenous pyelogram, done because of pyuria, was normal. Hemoglobin and white count were normal. Cerebrospinal fluid pressure was normal, no cells were present, and the protein was 235 mg. per cent on one occasion and 400 mg. per cent on another occasion. Blood Wassermann was negative. Electromyogram of the tibial muscles suggested anterior horn cell degeneration. She was fitted with bilateral drop-foot braces.

Since that time there has been slow progression of the weakness in her legs, with increased wasting of her leg muscles. There has been some wasting in her arms, some loss of weight, and considerable general failure. She has had repeated bouts of bladder infection with urinary frequency, but no retention or incontinence.

The patient is bright and cooperative and has above average intelligence. Her speech is normal.

Cranial nerves.

I. She is not able to recognize any test odor with either nostril.

II. She can read Jaeger 2 type with each eye. Examination of the left optic fundus reveals a normal disk and normal vessels, and the retina is covered with numerous small pigmented spots suggestive of "salt and pepper appearance." Only a poor view is obtained on the right fundus. There is marked general constriction of the fields of vision in both eyes, but tangent screen and perimeter were not used.

III, IV, and VI. Both pupils are pinpoint in size and slightly irregular. They both react slowly to light and convergence. There is fine well sustained nystagmus on right lateral gaze. The external ocular movements are full.

V and VII. Normal.

VIII. There is very severe perception type of deafness bilaterally.

IX, X, XI, and XII. Normal.

Motor system. There is marked generalized wasting of all muscles in the arms and legs, most marked in the distal muscle groups. The calf muscles are almost absent and there is considerable wasting of the forearm and intrinsic hand muscles. There is a generalized decrease in muscle tone. Muscle power is decreased in proportion to the wasting. There is complete bilateral foot drop. No spontaneous fasciculation is seen, but all muscles are irritable to direct percussion. There is slight impairment of coordination in both arms and legs, compatible with the weakness and sensory deficit.

Reflexes. It is possible to elicit a slight supinator reflex in both arms. Otherwise no deep reflexes can be elicited in arms or legs and no plantar response is obtained.

Sensory system. There is very marked impairment of temperature appreciation in both legs below the knees and in both hands. Vibration sense is absent below the iliac spines and present but decreased in the hands. There is no demonstrable impairment to pinprick or light touch in the arms or legs, and joint position sense is normal.

Stance and gait. Romberg test is negative. She walks quite well with bilateral drop-foot braces.

Peripheral nerves. No palpable enlargement of the ulnar or popliteal nerves.

REVIEW OF FAMILY PEDIGREE

In November 1954, 15 members of the family were examined (figure 3), including all the siblings and children of the two patients. A number of minor neurologic and other defects were noted or reported. The paternal grandfather (number 11 in pedigree) may have suffered from Refsum's syndrome, for he was reported to have been ill for a long time and died in his twenties. In spite of several consanguineous marriages, none of the children of the patients or their siblings were noted to have any neurologic defects, although none was over four years at the time of examination. The most striking abnormality, especially among the patients' siblings, is some degree of psychic abnormality. Two brothers were rejected from military service because of a "nervous" disposition, another brother is severely retarded, and a sister suffers from "nervousness."

DISCUSSION

There can be little doubt that these patients are suffering from a syndrome similar to that described by Refsum. Night blindness, atypical retinitis pigmentosa, and concentric constriction of the visual fields were early features. The patients went on to develop a chronic polyneuritis-like picture, with progressive weakness of the arms and legs, especially distally. Sensory changes included severe loss of sense of position in one patient and some peripheral blunting of pain and temperature in both cases. They both had marked nerve deafness. Severe ichthyosis occurred during their teens. Both had abnormal electrocardiographs, and both had a very high cerebrospinal fluid protein, with normal cell count. All these features are common to the cases described by Refsum. Urinary sphincter impairment was present in both our cases but absent in those of Refsum. The age of onset in our cases was earlier than in Refsum's original cases, who first developed symptoms during their twenties, but the syndrome has since been described in children.[2,3] The parents of our cases were first cousins, as were those in the various cases described by other authors.

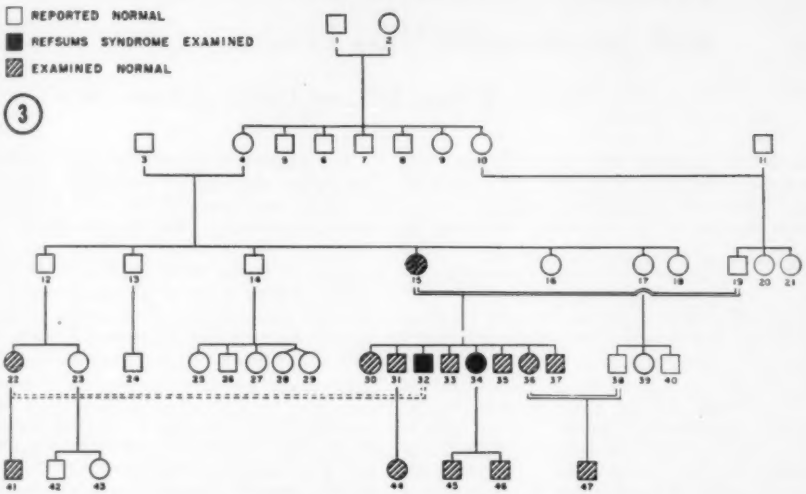

FIG. 3. Note consanguineous marriages (double lines). The parents of our two patients were first cousins. 3. Died at 35 of "galloping consumption." 8. Became blind early in life. 11. Was ill for a long time and died in his twenties. 14. Convulsions until the age of 25. 17. Sudden onset of right hemiplegia and aphasia postpartum at the age of 38. 19. Reported to have had severe nervousness, "neurasthenia," and very difficult temperament. 28 and 29. Twins; one died in infancy, the other one suffers from "severe nervousness." 30. Always "very sickly and nervous;" neurologically negative except for anisocoria. 31. Discharged from army because of nervousness. 33. Convulsions until the age of nine; rejected from navy because of nervousness. 37. Now age 18 and mentally retarded, with I.Q. of 74; has some dysarthria, but neurologic examination otherwise negative.

Among other members of the family were several with psychic abnormalities, an occurrence reported by Refsum and also seen in families with other hereditary neurologic diseases. Refsum reported epiphyseal dysplasia in the elbow, shoulder, and knee joints of his patients, but we did not note any such radiologic abnormality in the joints in our cases. Neither of our cases showed any sign of mental deterioration, though a brother was quite retarded mentally. In none of the cases described by other authors was there any mental deterioration.

There are several other familial or hereditary diseases that share some of the features seen in our cases. Hypertrophic neuritis (Déjerine-Sottas) may be confused with Refsum's disease, but the absence of palpably enlarged peripheral nerves, the high spinal fluid protein and the retinitis pigmentosa are much against that diagnosis. In the hereditary ataxias, retinitis pigmentosa and high spinal fluid protein are unusual and there are usually signs of pyramidal and extrapyramidal disease.

SUMMARY

Two siblings, whose parents were first cousins, developed progressive changes similar to those described by Refsum under the name "heredopathia atactica polyneuritiformis." These included retinitis pigmentosa, chronic polyneuritis with weakness, wasting and sensory changes in the limbs, progressive nerve deafness, and a high cerebrospinal fluid protein. Their history and findings are reviewed and the family pedigree is presented.

The author is indebted to Dr. Macdonald Critchley for the opportunity to study patient N. C. and for permission to publish the history. He is also indebted to Dr. H. J. Fenn of Great Bedwyn, Wiltshire, for his cooperation in studying the various members of the family.

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Erythrocyte Sedimentation Rate in Patients with Intracranial Mass Lesions

William K. Hass, M.D. and Donald H. Harter, M.D.

SINCE ITS INTRODUCTION by Fahraeus, the erythrocyte sedimentation test (ESR) has been used widely as a general screening test for systemic disease and as a guide in following the progress of a disease in a given patient.[1–4] The ESR has been assigned a less rewarding role as a "lead" in differential diagnosis.[5,6] This paper will present a review of results obtained when this test is used as an aid in differential diagnosis of proved space-occupying lesions in the cranium.

No attempt will be made to examine the possible reasons for abnormal rates; it will be our purpose instead to examine critically the assumption that the test can, with reasonable validity, aid in the prediction of the nature of an unknown intracranial mass.

METHOD

Available case records of patients with one of the six most commonly encountered intracranial mass lesions were examined. The lesions studied included brain abscess, astrocytoma, glioblastoma multiforme, meningioma, metastatic carcinoma, and subdural hematoma. In each instance, a survey period was chosen which would yield a statistically significant series. The smallest series, brain abscess, required the longest survey period, 1935-1956. All charts were examined within the chosen time period. Only initial sedimentation rates were evaluated. Cases were rejected that exhibited fever, pregnancy, or anemia. Also rejected were patients with coexistent systemic disease. Patients with carcinoma (usually bronchogenic) and brain abscess, however, whose systemic disease was solely the known or unknown primary lesion, were not excluded. All cases were verified by tissue examination.

In spite of the rigidity of the criteria, it was possible to select 558 cases. An interesting feature of the cases selected was that in general they were those most likely to present a differential diagnostic problem on admission.

The Westergren method for sedimentation rate determination was employed. Specimens submitted contained 0.5 cc. of 3.8 per cent sodium citrate and 2 cc. of whole blood. Only one hour values were reported.[7]

For purposes of practical clinical application the values obtained are compared with a rate of 20 mm. per hour which is taken as the upper limit of normality. This figure, though twice that originally favored by Westergren, agrees with more recent extensive studies of normal adults of both sexes in all age groups.[8,9] Because of the variable ratio of males to females in each series, it did not seem advisable to divide the patients into groups according to sex.

RESULTS

A statistical summary of all cases is presented in table 1. It may be noted that the average age in all diagnostic categories varied from 34 to 53. In each category there are individual values which range from normal to markedly elevated. Mean values, however, demonstrate marked group differences and tend to fall into three groups. Thus the ESR for astrocytoma and meningioma is well within normal limits. The mean rate in subdural hematoma and glioblastoma is borderline, while mean values for brain abscess and metastatic carcinoma are definitely abnormal. This relationship is graphically represented in figure 1.

Figure 2 analyzes the magnitude of the abnormal rates, that is, those exceeding 20 mm. per hour in each category. It will be noted that those lesions with the greatest proportion of abnormals also tend to exhibit relatively greater rates. Values in excess of 75 mm. per hour were found only in glioblastoma, metastatic carcinoma, and brain abscess.

Case records of patients with oligodendroglioma were also reviewed. When criteria for selection noted above were employed, the numbers yielded were considered too small for analysis. For sake of completeness, however, these rates are reported.

Eight male cases of oligodendroglioma exhibited rates of 2, 5, 9, 12, 15, 19, and 31 mm. per hour. Rates in 11 female cases were 2, 2, 5, 8, 10, 13, 15, 15, 18, 29, and 43 mm. per hour. These values parallel those reported for astrocytoma and meningioma. "Mixed" glial tumors were not included in the study.

From The Neurological Institute, Columbia-Presbyterian Medical Center, New York City.

TABLE 1
STATISTICAL SUMMARY

Nature of Lesion	Number of Cases			Average Age	Spread of Values mm./hr.	Mean ESR mm./hr.	Pct. Cases ESR greater than 20 mm./hr.
	Male	Female	Total				
Astrocytoma	50	36	86	35	1–72	8.8 ± 1.1	6%
Meningioma	35	66	101	49	1–68	13.3 ± 1.0	16%
Subdural hematoma	92	12	54	48	1–55	18.2 ± 1.8	37%
Glioblastoma multiforme	113	78	191	53	2–110	21.7 ± 1.4	39%
Metastatic carcinoma	72	22	99	53	3–124	30.3 ± 2.5	55%
Brain abscess	24	8	32	34	6–137	42.4 ± 5.5	69%

DISCUSSION

Three major studies[10–12] of ESR in intracranial mass lesions have been reported in the literature. In each the samples were in part too small and gave rise to certain inconsistencies which will be noted.

The first and perhaps still the most widely quoted study was that of Ask-Upmark who surveyed 93 cases of a wide variety of cerebral mass lesions.[10] In spite of an average value of 19 mm. per hour reported in four cases of metastatic carcinoma, the author concluded that, when the sedimentation rate (Westergren) is greater than 20, the lesion is "in most instances of malign character."

In 1940 Klingman, Laidlaw, and Spotnitz reported results (Westergren) in 125 cases of verified intracranial tumor and 43 psychoneurotic controls.[11] Their results in cases of astrocytoma, meningioma, glioblastoma, and metastatic tumors are in general agreement with the present report. Of interest, however, in this study was the finding of a relatively high average value (33.1 mm. per hour) for subdural hematoma and the additional notation that only one of a group of four brain abscesses ex-

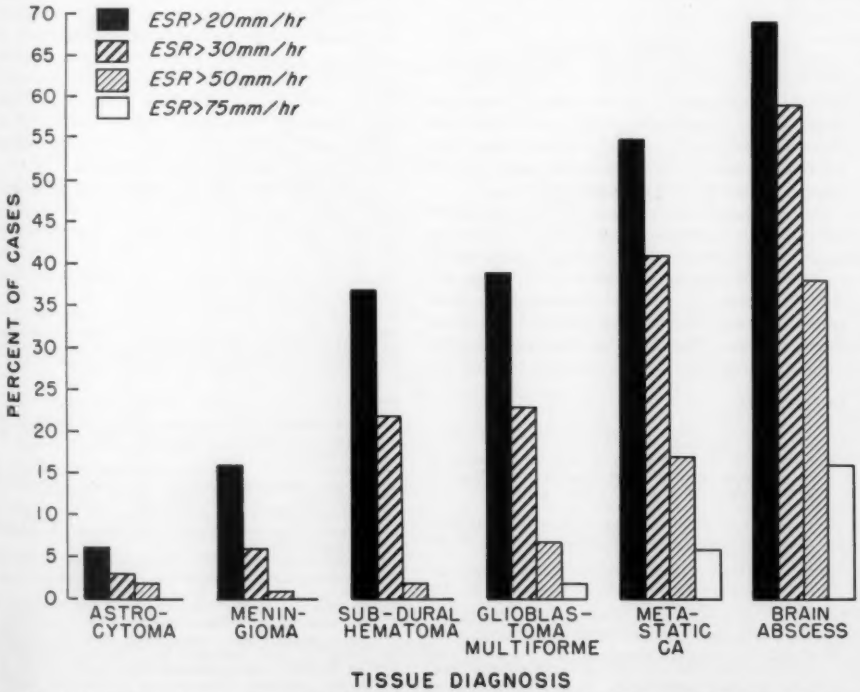

FIG. 1. Comparison of mean erythrocyte sedimentation rates. Each is presented with its appropriate standard error.

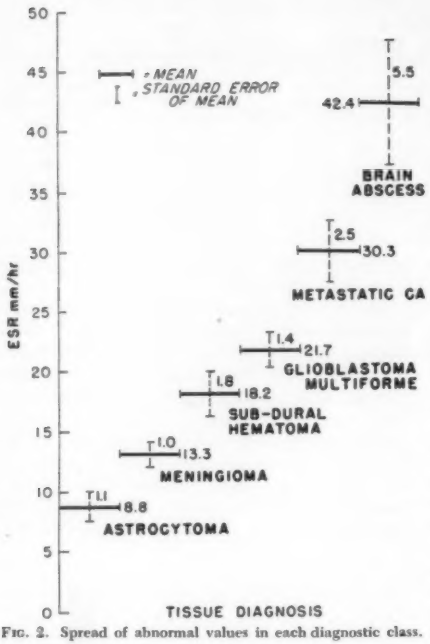

FIG. 2. Spread of abnormal values in each diagnostic class.

hibited an elevated (greater than 10 mm. per hour) rate. The obvious differences between these values and those of the present study are probably related to the small sizes of the groups reviewed in the earlier report.

More recently Frick and Folkers reviewed the German experience with ESR in brain tumors and reported values for 83 uncomplicated cases of glioblastoma multiforme.[12] These authors confirm the general finding that these rates are more likely to be greater than those found in less malignant primary brain tumors.

Our results bear out the current clinical impression based on previous reports that, in general, infectious and malignant lesions tend to exhibit greater numbers of abnormal sedimentation rates and higher abnormal values.

More specifically, the present data indicate that a low ESR will favor a diagnosis of astrocytoma or meningioma. Borderline to moderately elevated rates are most commonly found in subdural hematoma and glioblastoma multiforme. Markedly elevated rates are usually associated with brain abscess and metastatic carcinoma. Within each diagnostic class, however, normal and abnormal rates are found which disallow a categorical conclusion based on the ESR in any individual case.

SUMMARY

In order to determine the value of the erythrocyte sedimentation rate in the differential diagnosis of intracranial mass lesions, 558 cases of uncomplicated brain abscess, astrocytoma, meningioma, glioblastoma multiforme, subdural hematoma, and metastatic carcinoma were studied.

With 20 mm. per hour (Westergren) taken as the upper limit of normal, it was found that mean values for astrocytoma and meningioma were well within normal limits, while those for subdural hematoma and glioblastoma multiforme were borderline or moderately elevated. Brain abscess and metastatic carcinoma exhibited markedly abnormal mean rates. Rates within each diagnostic class, however, varied from normal to markedly abnormal.

It is concluded that the ESR is of some general value in predicting the nature of an intracranial mass. In any individual case, however, it should be specifically applied as part of the spectrum of information contributed by other clinical and laboratory methods.

The authors wish to thank Dr. H. Houston Merritt and Dr. Malcolm B. Carpenter for their helpful suggestions and assistance in the preparation of the manuscript.

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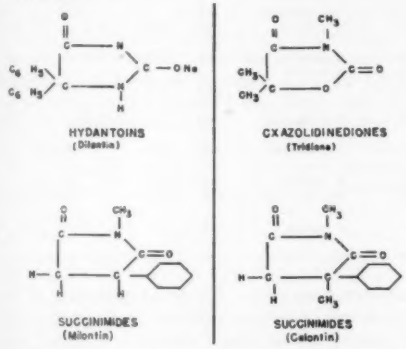
Use of Celontin in the Treatment of Mixed Epilepsy

Charles H. Carter, M.D. and Malcolm C. Maley, M.D.

CELONTIN (N-methyl-a,a-methylphenylsuccinimide), a new drug for the treatment of epilepsy, is related to other anticonvulsants as shown below:



Laboratory work[1] has demonstrated a wide spectrum of anticonvulsant activity in animals and this suggested a potentially broad range of action in convulsive disorders. Protection against supramaximal electroshock convulsions in cats and mice was afforded by doses of 100 mg. per kg. of body weight, while mice and rats were completely protected against pentylenetetrazole convulsions by 65 mg. per kg. of body weight. Anticonvulsants clinically effective in grand mal seizures confer protection to electrically-induced convulsions in animals; drugs effective in petit mal protect against experimental convulsions produced by pentylenetetrazole. Therefore, it seemed logical that Celontine might be useful in the treatment of both petit mal and grand mal. It was hoped that this drug would be effective against psychomotor seizures.

Studies by Zimmerman[2] on 54 patients suffering from petit mal demonstrated that Celontin produced a 55 per cent reduction of seizures and that complete control of seizures was achieved in 17 per cent, practical control in 17 per cent, and partial control in 36 per cent. From a further trial in which he treated 72 patients,[3] he concluded that Celontin is a drug of choice for petit mal. The dose used was 0.9 to 1.2 gm. daily. The same author also reported a 75 per cent reduction in seizures in 15 patients with psychomotor epilepsy.

So far no studies have been reported on the use of Celontin in institutionalized patients. Since such patients can be more carefully observed and their subsequent history more readily followed, it was felt worthwhile to set up a controlled trial on a small series of such cases. A further advantage is that the environment can be kept more nearly unchanged during the period of trial.

MATERIALS AND METHODS

The 16 patients in this study were all institutionalized in the Florida Farm Colony. Age, sex, and diagnosis are given in table 1. Diagnosis was based on clinical criteria, supported by an electroencephalogram. Complete hematologic studies, urinalyses, and liver function tests were performed monthly. All patients had been under observation and their seizures carefully recorded for 12 months prior to starting medication. Living conditions and social environment were constant throughout the control and treatment periods.

The dosage employed was 0.3 to 1.8 gm. of Celontin administered orally and in divided dosages two or three times daily. As therapeutic effect and tolerance varies with anticonvulsants from patient to patient, the dosage was individualized to the requirements of the patient. In the early stages of the trial while experience with the new drug was being gained, dosage was less than that subsequently employed when it was realized that the drug produced few side effects. Therefore, the optimum dose, producing the maximum of seizure control with the minimum of side effects, may not have been employed in all cases.

RESULTS

The findings for individual patients are recorded in table 1. In 15 of the 16 patients there was a reduction in both petit mal and grand mal attacks. Grand mal attacks were completely controlled in two, practical control

From Florida Farm Colony, Gainesville, Florida.

TABLE 1

EFFECT OF CELONTIN ON THE FREQUENCY OF SEIZURES IN 16 PATIENTS WITH MIXED EPILEPSY

Patient	Age Sex	Diagnosis	Control Period Duration (months)	Control Period Average monthly seizure rate Grand	Control Period Average monthly seizure rate Petit	Treatment Period Duration	Treatment Period Average monthly seizure rate Grand	Treatment Period Average monthly seizure rate Petit	Dosage (daily)
G.B.	14 M	GM, PM.	12 months	37	3	2½ months	7	0	0.6 gm.
W.C.	7 M	GM, PM.	12 months	131	17	2½ months	19	5	0.9 gm.
J.C.	18 F	GM, PM. Psych.	12 months	109	77	17½ months	16	50	0.9 gm.
G.D.	30 F	GM, PM. Psych.	12 months	83	19	9 months	28	4	0.9 gm.
M.F.	31 F	GM, PM.	12 months	41	11	1 month	2	0	1.8 gm.
R.G.	13 M	GM, PM.	12 months	51	7	1½ months	17	3	0.9 gm.
L.H.	31 F	GM, PM. Psych.	12 months	28	17	10 months	86	20	0.3 to 1.8 gm.
B.L.H.	22 F	GM, PM.	12 months	71	14	2 months	4	2	0.9 to 1.8 gm.
J.J.	20 F	GM, PM.	12 months	2	6	2 weeks	0	0	0.9 gm.
E.J.	20 M	GM, PM. Psych.	12 months	28	38	10 months	12	2	0.3 gm.
J.L.	20 F	GM, PM. Psych.	12 months	144	62	3½ months	92	37	0.3 to 1.8 gm.
Z.M.	17 F	GM, PM. Psych.	12 months	40	5	2½ months	0	0	0.9 gm.
G.N.	44 M	GM, PM.	12 months	40	34	2 months	4	0	1.8 gm.
B.N.	18 F	GM, PM. Psych.	12 months	49	19	5½ months	1	3	0.3 gm.
P.S.	13 F	GM, PM. Psych.	12 months	157	15	1 month	2	1	0.99 gm.
E.W.	25 M	GM, PM.	12 months	96	45	2½ months	53	21	0.9 to 1.8 gm.

(reduction of 50 per cent or over) was achieved in 11, some reduction in two, and in one patient the attack rate was increased. Complete control of petit mal seizures was obtained for five patients, practical control for eight, some reduction for two, and in one patient the attack rate was increased. The eight patients suffering from psychomotor epilepsy showed a substantial reduction in attacks almost amounting to complete control.

Results for all patients taken together indicated that the monthly seizure rate was reduced from 1,107 to 343 in the case of grand mal and from 389 to 148 in the case of petit mal. This represents a 65 per cent reduction in grand mal seizures and a 57 per cent reduction in petit mal seizures.

SIDE EFFECTS

The only side effect noted was drowsiness experienced by five patients. This disappeared on reducing the dosage. Routine liver function, urine, and hematologic tests were normal.

DISCUSSION

Laboratory experiments on animals suggested that Celontin would be an effective drug for the treatment of petit mal, grand mal, and psychomotor epilepsy. Clinical experience in the treatment of these conditions confirms its value. It would appear that Celontin is a useful anticonvulsant drug.

It is felt that a trial on institutionalized patients has many advantages. An accurate record of the frequency of attacks can be kept by trained staff. Side effects may be observed more readily, and the patient is always available for routine laboratory tests. Furthermore, the changes in environment which frequently alter the seizure rate may be minimized.

SUMMARY

1. Celontin was administered to 16 patients suffering from grand mal, petit mal, and psychomotor seizures occurring either singly or in combination. All patients were in an institution where they could be observed carefully.

2. By comparing the monthly seizure rate following treatment with that of the preceding 12 months, it was demonstrated that Celontin was an effective drug in the control of petit mal, grand mal, and psychomotor epilepsy.

3. No significant changes were observed in hematologic, liver function, and urine tests, and the only side effect noted was drowsiness.

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Procyclidine Hydrochloride (Kemadrin) Treatment of Parkinsonism

Result in 108 Patients

Adolfo Zier, M.D. and Lewis J. Doshay, M.D.

CONFLICTING VIEWS prevail with regard to the need for new drugs in the treatment of parkinsonism. Those who work with large numbers of these sufferers find that there is a great need for new and better remedies,[1] because 1) drugs tend to wear off in effect with the passing of time as the patient's tolerance rises; 2) some drugs exert a potent action against tremor but little, if any, against rigidity, inertia, muscle cramps, or mental depression so that many patients require three, four, or even five drugs at the same time in order to combat all the symptoms; 3) parkinson cases are increasing in number as a consequence of the lengthening span of life;[2] 4) some patients tire of any remedy during the long siege of the illness and good substitute preparations must be available to them.

We report here our observations with a new drug that has been added to the therapeutic armamentarium for parkinsonism, procyclidine hydrochloride (Kemadrin). It was first synthesized and studied in England[3] and introduced in this country in 1953.[4] Our investigation of its usefulness in the therapy of paralysis agitans commenced in April 1954.

CHEMISTRY

Procyclidine hydrochloride (Kemadrin) is 1-cyclohexyl-1-phenyl-3-pyrrolidino-propan-1-01. It is a spasmolytic agent that is chemically and pharmacologically related to trihexyphenidyl (Artane). As with trihexyphenidyl, it has an atropine-like parasympatholytic action.[5] In rabbits it abolished the tremor resulting from nicotine toxicity, which some authorities[6] regard as an index of the control of parkinson tremor. There were minimal or no effects on blood pressure, heart, respiration, or hematologic components among the animals studied.

MATERIAL AND METHOD

We have investigated the action and side effects of procyclidine in a series of 108 parkinson and 8 non-parkinson patients. Among the parkinson cases, 27 were of the postencephalitic, 36 of the idiopathic, and 45 of the arteriosclerotic variety. The patients were unselected, except as they had failed to respond to or expressed dissatisfaction with standard antiparkinson remedies. The nonparkinson cases included patients with double athetosis, Huntington's chorea, senile tremor, dystonia musculorum deformans, and familial tremor. Ages ranged from 22 to 75 years, and males predominated over females in the series to the extent of 63 to 37 per cent. Most of the patients had been under previous treatment with such preparations as 0.5 per cent atropine solution, Bellabulgara, Rabellon, hyoscine, Artane, Pagitane, Cogentin, Parsidol, Benadryl, Thephorin, and Dexedrine.

In some cases, procyclidine was added in increasing doses as other drugs were gradually removed; in other cases, the new drug was added to the existing regimen; and in still others, it was promptly substituted for the latter. No disturbing effects were noted from the sudden substitution of therapy.

At the outset of our study, patients were started on 10 mg. doses three to six times a day, but this was found to provoke complaints of excess dryness, restlessness, and mental fogginess in some patients, so that in subsequent trials we commenced with 2.5 mg. three times daily and this was increased to maximum tolerance. In this way fewer and less disturbing side reactions were encountered. The optimum maintenance dosage for younger patients was found to be 10 mg., three times daily, and for older patients 5 mg. three times daily, although there were many instances of elderly people who tolerated 40 to 60 mg. per day without complaint. The drug is best administered after meals and avoided at bedtime. The duration of action is four to six hours and some degree of dryness usually appears within one hour.

Cogentin was added at bedtime for cases with severe rigidity, contracture, and muscle cramps, and Parsidol by day if there was ex-

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TABLE 1

RESULTS OF TREATMENT WITH PROCYCLIDINE HYDROCHLORIDE (KEMADRIN) IN 108 PARKINSON AND 8 NON-PARKINSON CASES

	Totals	*Improved*	*Unimproved**
Parkinson cases			
Postencephalitic	27	13 (48%)	14 (52%)
Idiopathic	36	18 (50%)	18 (50%)
Arteriosclerotic	45	31 (69%)	14 (31%)
Totals	108	62 (57%)	46 (43%)
Non-parkinson cases			
Senile tremor	3	3	
Huntington's chorea	2	2	
Double athetosis	1	1	
Dystonia musculorum	1		1
Familial tremor	1		1
Totals	8	6	2

*This heading includes 10 patients who claimed they were made worse by procyclidine hydrochloride.

cess tremor. In 10 per cent of the patients, procyclidine was used along with Artane as it seemed to potentiate the action of the latter drug. Some patients received placebo tablets of similar appearance to the new drug, and other patients were required to withdraw procyclidine for a week at a time in order to afford comparisons of the effects and side reactions.

RESULTS

The criteria for success or failure in this study rested upon reports from the patient and family with regard to the activities of daily life, covering items of work, self-care, gait, speech, alertness, and so on, and upon clinical observation of changes in the patient during visits to hospital and clinic.

A patient was regarded as improved if one or more of the cardinal symptoms of parkinsonism[7] had shown improvement and this improvement lasted for at least one month. Cases were listed as unimproved if the drug failed to control at least one of the basic symptoms of the disease, or if the side reactions were intolerable at the therapeutically effective level.

The results with procyclidin therapy were highly gratifying. Of the 108 parkinsonian patients, 62 or 57 per cent responded favorably (table 1). Unimproved cases accounted for 46 or 43 per cent of the series, among which were ten patients who claimed that their symptoms were made worse by this drug. Procyclidine afforded striking results in six of the eight non-parkinson dyskinesia cases, and one of them, a double athetosis patient, improved so much in the course of six weeks that he was able to carry on successfully without further medication.

Procyclidine was found to be better tolerated by and of greater benefit to arteriosclerotic than post-encephalitic patients (69 to 48 per cent). It proved efficacious in the control of rigidity, tremor, akinesia, fatigue, weakness, and mental depression. It also afforded a feeling of general well-being to 19 (18 per cent) of the patients (table 2).

Of the entire series of 116 cases, 42 patients (36 per cent) were maintained on procyclidine alone, while in 74 (64 per cent) the new drug was used along with other preparations. The drug readily combines with any of the antiparkinson agents and was so employed in 28 per cent of the cases with Cogentin, in 10 per cent with Artane, in 7 per cent with Benadryl, in 7 per cent with Dexedrine, in 6 per cent with Parsidol, and in 6 per cent with Pagitane.

In a number of patients, the favorable effects of procyclidine wore off with the passing of time, as in the case of most remedies,[8] and such patients had to be switched to other treatment. Even so, 27 or 44 per cent of the successful cases have continued with procyclidine for over six months. The fact that 44 per cent of the improved patients, who had had previous experience with Artane, Pagitane, and other good antiparkinson agents, chose to continue with procyclidine for over six months is in itself an indication of its intrinsic value to them. By comparison, we have tested many new experimental drugs that had to be re-

TABLE 2
INDIVIDUAL SYMPTOMS IMPROVED BY PROCYCLIDINE HYDROCHLORIDE

*Improved Symptoms**	*Number of Cases*	*Per Cent of Total Number of Cases (116)*
Rigidity	41	35%
Tremor	40	34%
General well-being	19	16%
Gait, posture, and balance	12	10%
Adynamia	10	9%
Sleep	7	6%
Akinesia	6	5%
Speech	4	3%
Sialorrhea	2	2%
Oculogyric crises	1	
Chorea movements**	2	
Athetoid movements***	1	

*Most of the improved patients responded with improvement in more than one of these symptoms.
**From cases of Huntington's chorea. ***From case of double athetosis.

jected because 70 to 90 per cent of the patients discontinued their use within a few days to several weeks.

SIDE REACTIONS

The types of side effects from the use of procyclidine were similar to those encountered with other antiparkinson agents.[9] The intensity of the reaction was greater during the early stages of our study when large doses were employed but became less so when the amount of medication was reduced to suit the individual tolerance and needs of the patients. No serious reactions appeared among any of the cases.

The most common side effects were dryness of the mouth, blurring of vision, and giddiness. The dryness reaction was notably less than with the natural and other synthetic compounds. A small number of patients complained of weakness, nausea, restlessness, and insomnia. There were no instances of mental confusion, delirium, or hallucinations, even among elderly patients who took as much as 60 mg. a day.

In many patients, the side reactions from procyclidine progressively diminished in number and intensity as the administration of the drug was continued, frequently within two weeks to a month. Most of those who stopped the medication because of unfavorable side-effects did so within the first few days of treatment. Complete blood counts made in a number of patients failed to disclose any abnormal changes.

REPORT OF CASES

Cases will be cited to illustrate points of significance in the posology, method of administration, and actions of procyclidine (Kemadrin):

Case 1. A 72 year old woman weighing 105 pounds has suffered with arteriosclerotic parkinsonism for eight years. The illness steadily progressed to involve the trunk and limbs, with severe rigidity, akinesia, muscle cramps, and tremor. Artane had provided relief for three years, but the effects wore off. In August 1953 she was switched to Pagitane (antispasmodic 08958) and Cogentin (MK-02). She felt better except for tremor, for which Parsidol was added. She fared well on this program until early 1955, when the symptoms again became troublesome and she had no energy. Dexedrine was tried in small doses without effect, and in larger doses served to aggravate the tremor. In May 1955 she was switched to procyclidine (Kemadrin), 10 mg. four times a day. The effect was dramatic. She began to move with greater ease, felt stronger in body, and the tremor was almost completely controlled. She did not experience any dryness, blurring, dizziness, or drowsiness and on her own increased Kemadrin to 20 mg. three times a day. In September 1955 a 2 mg. tablet of Cogentin was added at bedtime for the control of cramps in the legs. She has continued to do well to the present. She is a spirited woman and, despite her disabilities, is active at home and travels with her husband to far places, even to Europe.

Case 2. A heavy-set 37 year old man with postencephalitic parkinsonism, with rigidity, tremor, and a speech impediment, had been on a wide assortment of remedies, the last Artane. He was sensitive to most drugs and accordingly derived limited value from them. In April 1956 he was

started on 2.5 mg. of Kemadrin three times a day. It helped his tremor, improved his speech, and provided him with a feeling of well-being. He recurrently complained of dizziness and dryness of the mouth, yet wished to continue with the preparation because of the positive benefits. Under the circumstances, it was not considered advisable to chance increases in medication. His improved physical state has maintained to the present.

The above cases serve to point up the importance of fitting the dose to the individual. On the one hand, we note an elderly frail woman tolerating 20 mg. of procyclidine three times a day without a trace of side reaction; on the other hand, a much younger and sturdier patient was barely able to tolerate 2.5 mg. three times a day.

Case 3. A 52 year old man gave a history of psychiatric symptoms treated by shock therapy in 1952, following which symptoms of parkinsonism appeared. Rigidity involved the entire body, with drooping of the head, propulsive gait, and contractures at the ankles, elbows, and shoulders. He had tried Rabellon, Artane, Cogentin, and Parsidol and found it necessary to discontinue each because of side-reactions. In March 1954 he was given 5 mg. of Kemadrin three times a day and reported greater relief from tremor, rigidity, and akinesia than from all previous medications. He has remained on this dosage to date and employs no other medication than Kemadrin. He states that it controls not only his somatic tremors but also his visceral tremors and that it has completely done away with muscle cramps in his legs.

The above case shows how Kemadrin alone can provide relief from all the symptoms of parkinsonism.

Case 4. A 53 year old pharmacist suffered from a rapidly progressive idiopathic parkinsonism of five years' duration. Tremor and rigidity commenced in the right arm and leg and spread to the trunk and left side to a degree where he was no longer able to work, found walking difficult, and needed help in dressing, feeding, and personal hygiene. He had on his own experimented with a great assortment of medicaments, among them Bellabulgara, Artane, Benadryl, Pagitane, Parsidol, Genoscopolamine, and phenobarbital. He discontinued each in quick turn, because of excess dryness, difficulty in swallowing, drowsiness, dizziness, impaired vision, or queer sensations in the head and one time because of a feeling of an "impending stroke." Treatment with Cogentin was started in March 1955 but was discontinued because of dryness and weakness. He discontinued hyoscine because of unbearable mental fogginess, Meratran because of internal cramps, and Thephorin because of dopiness and frequent urination. On June 2, 1955 he was tried on 2.5 mg. Kemadrin three times a day. He discontinued this within three days on complaint of severe palpitations.

Here we note an instance of the hypersensitive, discouraged, and neurotic individual who failed on procyclidine as well as other drugs through one complaint or another.

Case 5. A 77 year old man with arteriosclerotic parkinsonism gave a long-standing history of diabetes and progressive rigidity, tremor, and slowing of gait and speech of five years' duration. He had been on Artane and Dexedrine until 1954, when it was found necessary to switch him to Pagitane. He complained of increasing nervousness, tremor, and night terrors, for which Parsidol was added. He discontinued the latter because of drowsiness. Reserpine was tried but had no effect. In March 1955 he was started on 5 mg. of Kemadrin three times a day. He found greater strength and the tremor eased so that he was able to shave and feed himself with greater steadiness. The night terrors disappeared. Two months later a tablet of Cogentin was added at bedtime to counteract cramps in the toes. He has continued to do well on the above program and at his last visit, September 6, 1956, reported that he felt much better on Kemadrin than on Artane or Pagitane, that he experienced less dryness of the mouth, his appetite is better, the flow of urine is freer, he has more energy to conduct his work, and suffers no mental fogginess.

In this case we observe the potent action of procyclidine against a variety of symptoms and the lasting nature of the effects without increase in dosage or tolerance.

DISCUSSION

Procyclidine (Kemadrin) is not a panacea. Yet in our experience it proved a worthy addition to the therapy of parkinsonism, because it afforded relief to many patients who had failed to respond to other drugs. It exerts an action against all the symptoms of parkinsonism, including rigidity, tremor, akinesia, fatigue, sialorrhea, and mental depression; hence it may be employed as the basic drug in commencing treatment with new cases. If rigidity is too severe Cogentin[10] may be added, and if tremor is of major proportions Parsidol[11] may be added. Procyclidine afforded striking help to patients with basal ganglia disease other than parkinsonism. This action deserves further exploration.

Procyclidine produces only minor side-reactions and is safe to use in young and old patients. In fact, it was found better tolerated by older patients and more effective among them than among the comparatively younger postencephalitic cases. This bears significance, since we are seeing fewer and fewer younger parkinsonian patients and increasingly greater numbers of the older cases. Thus, antiparkinson medications of the future will necessarily have to be geared more and more to the tol-

erance of this group. It should also be apparent that there will be a continued need for new and better medicinal remedies than we now possess, because of the known hypersensitivity of older patients to many drugs,[2] because the prospect of relief by surgical therapy for this age group is a very remote possibility,[12] and because in the process of aging these patients accumulate a multiplicity of the severest symptoms.

SUMMARY

A series of 108 patients with parkinsonism and eight patients with other types of dyskinesia, all of whom had failed to respond to standard antiparkinson remedies, were treated with procyclidine hydrochloride (Kemadrin) over a period of two years. Of the parkinsonian cases, 57 per cent showed improvement in symptoms and well-being and 43 per cent were unimproved. The drug was found especially helpful in older arteriosclerotic cases. The side-reactions were generally milder than with other drugs employed in the treatment of this ailment. Procyclidine is closely related structurally and pharmacologically to Artane and exerts an action upon all the symptoms of parkinsonism. It may, therefore, be employed as the basic drug in commencing treatment with new cases, to which other drugs may be added as required. It may readily be used in combination with current antiparkinson preparations. It was found highly beneficial to six of the eight cases with non-parkinson dyskinesia symptoms. Our findings indicate that procyclidine is a valuable addition to the treatment of parkinsonism and other conditions with abnormal movements.

Procyclidine hydrochloride in the form of Kemadrin was furnished for the study by Burroughs Wellcome and Co., Tuckahoe, N. Y.

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■ I suppose no one nowadays would confess to a belief in a faculty of coordination, nor to a belief in a co-ordinating centre, but that all consider every nervous centre, whether spinal, cerebellar, cerebral or sympathetic, to be a centre of co-ordination, and that only in the sense of its being a part where these or those impressions and movements are represented in this or that degree and order. So those who hold that the cerebellum is the centre for the most special and complex co-ordinations of locomotor movements mean that it is a centre where the most special and complex of these movements are represented. This is only another way of saying that the cerebellum represents specially those movements which are bilateral or alternate. If we take count of all kinds of locomotion and, indeed, of equilibration, whether statical, as in standing, or continually changing, as in progression, we see that the usual statement as to the chief functions of the cerebellum is equivalent to saying that it represents movements of all parts of the body. We must not use the term locomotion for walking only. In swift running the body is bent forwards, the jaws and face are in action, the arms swing, and professional runners carry cork in their hands to prevent the nails hurting the palms. We have to study all degree of locomotion, from getting up to swift running, with the aim of ascertaining the order in which movements of different parts of the body are represented in the cerebellum.—J. Hughlings Jackson in *On Tumours of the Cerebellum*, published in 1881.

Electrical Activity of Rolandic Region in Unanesthetized Monkey

Lawrence Kruger, Ph.D. and Charles Henry, Ph.D.*

ALTHOUGH the Rolandic cortex of primates has often been regarded as a functional unit, a variety of experimental procedures has led to the demonstration of numerous differences between the precentral and postcentral cortical fields. These regions are known to differ markedly in cellular structure and in the relative preponderance of somatic afferent and efferent fibers, and they react differentially to electrical stimulation. The spontaneous electrical activity of this region, however, has received less intensive study.

The predominance of fast activity in the sensorimotor region of cats was established by Rheinberger and Jasper[1] and Clark and Ward[2] with the use of implanted electrodes, but their technic did not enable precise areal differentiation in this region. Kornmuller,[3] however, reported differences in the spontaneous electrical activity of minutely differentiated cytoarchitectonic areas in rabbit and monkey, a finding which has had little support and indeed is contradictory to the observations of Garvin and Amador[4] on the monkey.

The human electrocorticogram has been studied by several investigators,[5–9] with few findings significant for precise areal differentiation. However, Scarf and Rahm,[5] Jasper and Penfield,[7,8] and Marshall and Walker[9] have reported that beta activity predominates in the frontal lobes anterior to the central fissure and that alpha activity predominates posteriorly. Jasper and Penfield[7] also reported a blocking of beta activity accompanying movement. Because of the functional importance of these findings in man, we have attempted to extend these finding to the unanesthetized monkey by using implanted electrodes. The additional advantages of such experiments are that a larger series can be studied for long periods of time in the absence of any drug effects, that one is recording from a brain in which the homologies are well known, and that there is absence of pathology or the surgical effect of cortical exposure.

MATERIALS AND METHODS

Six adolescent monkeys (*macaca mulatta*) were used in these experiments. In each animal a plate electrode was placed with six recording points arrayed longitudinally in the leg area of the Rolandic cortex. The electrodes were constructed according to the method described by Delgado,[10] with electrode points oriented in linear fashion and spaced 2 or 5 mm. apart. In two animals additional electrodes were placed in other areas.

All animals were anesthetized with Nembutal (30 mg. per kg.) for implantation of electrodes. A linear midline longitudinal scalp incision was made and bone opened just widely enough to expose the dura over 1 cm. in either direction from the central sulcus. The plate electrode was placed on cortex, with points numbered 3 or 4 closest to the fissure, point number 1 always anterior in the precentral region, and point number 6 most posterior on the postcentral gyrus. The dura was closed tightly over the electrode and the shaft sutured to bone at two points with wire. The scalp was sutured in two layers with the plug protruding from the posterior end of the wound. Electrode orientation was checked with x-rays (figure 1).

Records were taken on a six channel Offner crystograph, supplemented by a cathode ray oscilloscope and Grass camera. In addition to recording from the implanted electrodes, needle leads were inserted into the scalp and muscles of the legs. All animals were restrained in a wooden box which gave easy access to the head and legs. With some animals it was also necessary to restrain head movements by taping the head to the box.

In one animal, alumina cream was injected into the precentral cortex beneath the recording electrodes in the manner described by Kopeloff and associates.[11] Tactile stimuli were applied to the hairs with a small camel hair brush mounted on a solenoid driven by an electronic pulse generator.

RESULTS

Spontaneous Activity

The outstanding feature of the electrical

From the Institute of Living, Hartford, Connecticut.
Read at a meeting of the Eastern Association of Electroencephalographers, September 30, 1955.
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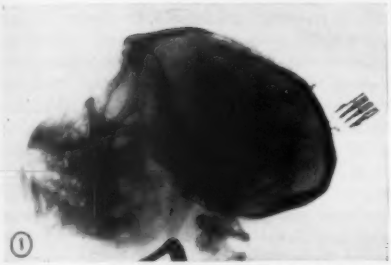

FIG. 1. The position of the six recording points can be seen as black dots in the roentgenogram of the dorsal bone defect in the central region.

activity in the Rolandic region was the abundance of low-voltage fast activity present in each animal. Although individual differences were clearly present, a rhythmic pattern of 25 to 30 per second was seen routinely, most prominently in records from the precentral gyrus; amplitude rarely exceeded 25 microvolts. There was also much semi-rhythmic fast activity up to 45 per second recorded maximally from electrodes anterior to the central fissure (figure 2). In general, slower activity was seen from postcentral leads, consisting of irregular complex three to about eight per second activity. At times, small groupings of clear eight per second alpha activity were detected in the posterior leads in two of the animals. Although precentral and postcentral activity differed in the predominance of fast and slow activity, the central fissure can be regarded only as an approximate border; the transition is probably best conceived as an anteroposterior gradient. This gradient is often accentuated by the reduction of amplitude in records from the leads closest to the central fissure, a finding which may be due to the presence of a large blood

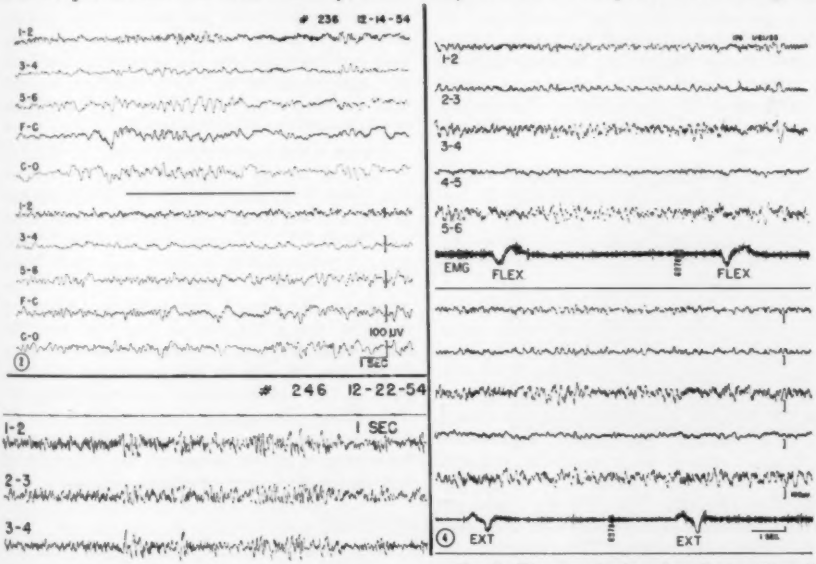

FIG. 2. The upper tracings show the transition of the spontaneous activity from precentral (1–2) to postcentral (5–6) and frontal to central (F–C) and central to occipital (C–O) scalp recording during the onset of drowsiness with the animal's eyes closed. In the lower tracings, the same recording conditions prevail, but the animal is alert with eyes open. Note the resemblance of the scalp and postcentral corticographic activity and the predominantly faster precentral activity which is difficult to detect with scalp recording.

FIG. 3. The electrical activity of the Rolandic region during natural sleep showing the predominance of 15 to 18 per second sleep spindles anterior to the central fissure in leads 1 to 3.

FIG. 4. The upper tracings show the burst of fast activity in the Rolandic region during flexion of the contralateral ankle; the lower tracings show the same effect during extension of the ankle. The induced fast activity is best seen in records immediately in front of the central fissure (3–4), but is also detected in postcentral records (5–6).

vessel between recording points.

Scalp recordings from the central region bear only a slight resemblance to the corticogram recorded from the pial surface. The low voltage fast activity is less discrete in the scalp records, whereas the three to eight per second postcentral activity seems to dominate the pattern recorded from the scalp in this region (figure 2). It is also noteworthy that muscle artifact recorded in scalp leads was rarely detectable from the cortical electrodes.

Sleep Patterns

With the onset of drowsiness, the postcentral records displayed higher voltage slow waves and five to eight per second activity (figure 2) which immediately disappeared if the animal opened his eyes. If the animal continued in the drowsy state, however, this slow activity spread to the precentral region and tended to replace the usual fast pattern. In deeper sleep (rare in our animals) a clear spindling of 15 to 18 per second appeared maximally in the precentral region (figure 3). In some records, sleep activity appeared to reverse in phase from precentral to postcentral in the electrocorticogram as well as in the scalp electroencephalogram.

Alteration of Activity Patterns by Movement

Movement of the leg contralateral to the implanted electrode was accompanied by a distinct alteration of the spontaneous activity recorded from Rolandic leads. The effect consisted of a blocking of the usual rhythmic activity and the appearance of a 50 to 80 per second pattern (occasionally faster) of about one second duration (figure 4). This effect was often most clearly observed in the posterior part of the precentral gyrus, but was also present in the anterior precentral and postcentral cortices. It occurred with either spontaneous ("voluntary") movement or manually induced movements of the appropriate joint in any direction. The rhythmic fast activity rarely exceeded two seconds in duration, even with prolonged strong contraction. The onset of the induced cortical activity appeared to either coincide with or follow the simultaneonsly recorded electromyogram, but it is conceivable that some muscle activity precedes the cortical fast activity which is not detected with the present myographic technic. The induced fast activity of the Rolandic leg area was seen only with movements of the contralateral leg, that is, movements of the ipsilateral leg or either arm did not produce any obvious alteration in cortical activity.

Under barbiturate anesthesia (Nembutal or Dial) there was no detectable change in cortical activity associated with movement, if one excludes responses to cutaneous stimulation. However, when the animal emerged from barbiturate anesthesia there was a clear fast barbiturate pattern of about 25 per second, recorded maximally just anterior to the central fissure. With movement, a higher voltage rhythm of about 35 per second appeared in the precentral and postcentral cortex with its maximum amplitude precentrally (figure 5).

Responses to Tactile Stimulation

Displacement of a few hairs on the leg elicited a distinct short latency surface positive cortical wave (the classic "tactile evoked response") without any other obvious alteration of cortical activity. These evoked potentials were often obscured by spontaneous activity, but were readily identified with repetition. Such responses were consistently recorded in the postcentral gyrus only. The peripheral receptive field of a postcentral point was well circumscribed in the unanesthetized animal and consisted of a very restricted area of skin on the contralateral leg. No ipsilateral tactile responses were observed.

Under deep barbiturate anesthesia (Dial or Nembutal) tactile responses from the postcentral gyrus were more easily observed because of the marked reduction in spontaneous activity (figure 6). The other effects of anesthesia were a prolongation of onset and peak latencies (about seven milliseconds) and an increase in the size of the peripheral receptive field on the contralateral limb, so that the same cortical point could be activated by a larger area of skin in the deeply anesthetized than in the unanesthetized animal. However, this difference may be questionable, since responses from the periphery of the receptive field may easily be obscured by spontaneous activity in the unanesthetized animal.

DISCUSSION

It is clear from the present study and previous observations on man[7] that the central fissure forms an approximate boundary for the slower activity recorded from the parietal and occipital cortex in primates. This boundary is not a sharp demarcation point but rather consists of a region of maximal transition in a continuous gradient of spontaneous electrical activity. The remarkably fast activity recorded maximally in the precentral region appears to differ somewhat from that seen in man. First, it usually lacks the clearly sustained rhythmic character of the precentral beta ac-

tivity in man; this might be expected in monkeys since they rarely show long periods of distinct alpha activity. The second finding is the extremely high frequency activity, often about 80 per second with the onset of movement. It is presumably not due to contamination by muscle action potentials since it does not correlate with scalp leads in this region, nor can it be elicited by movements of parts of the body other than the appropriate contralateral limb. Irritative effects due to the presence of a foreign body chronically implanted on the pia might possibly induce this fast activity. However, in one animal with alumina cream injected into the cortex beneath the electrode to simulate cortical irritation, the most striking finding was the rapid obliteration of all fast activity and gradual development of high-voltage slow waves appearing in seizure patterns (figure 7). Consequently, it seems more likely that this fast pattern is normal cortical activity rather than an effect of scarring. Its relative absence in human electrocorticograms and the records in monkey obtained by Garvin and Amador[4] may be due to deleterious effects of exposure of the cortex while recording.

The relation of spontaneous electrical activity to cortical structure is difficult to determine because of the problems inherent in determining criteria to be used in demarcating the continuous gradients of electrical as well as cellular patterns. The abrupt transition in the depths of the central fissure from a precentral "agranular" cortex with many large cells to a postcentral granular cortex with few large cells makes this region of the macaque brain a most likely place to detect changes related to cytoarchitectonics. Most previous studies emphasize the essential similarity of the granular and agranular cortex of the sensorimotor region in that fast activity of 20 per second or higher is usually seen only in this region of the cortex,[1,2,4] but Kornmuller[3] emphasized that the "precentral agranular" field of the rabbit and monkey cortex showed somewhat faster activity than the "postcentral" cortex.

His records from the rabbit cortex clearly demonstrate this point and the records from monkey cortex published by Garvin and Amador[4] might be interpreted similarly. However, it must be emphasized that the subdivision

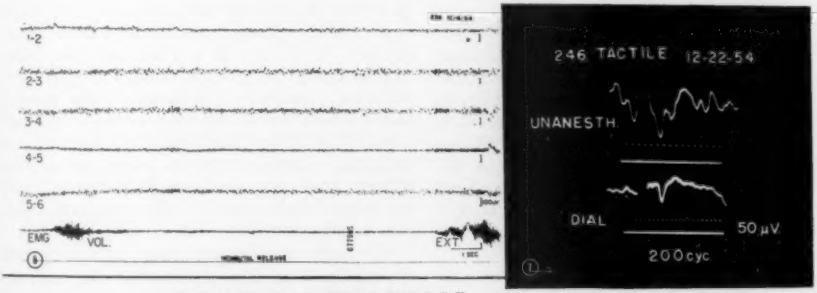

FIG. 5. Recordings of barbiturate activity of about 23 per second in the Rolandic region in an awake animal that had been anesthetized with Nembutal several hours earlier. Under this circumstance the rhythmic activity accompanying voluntary and induced movement increases in amplitude as well as in frequency. The effect of movement is again best seen in precentral records (2–3 and 3–4).

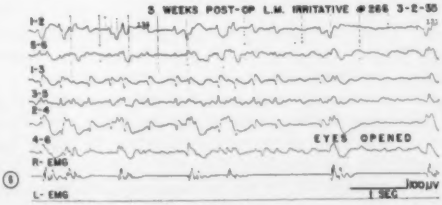

FIG. 6. The postcentral electrical response to tactile stimulation of the contralateral foreleg with a small camel hair brush. The baseline is blanked during the excursion of the solenoid driving the brush. The upper record was obtained in the unanesthetized animal; the lower tracing is a record from the same cortical point with the animal under deep Dial anesthesia. The onset and peak latencies are prolonged by seven milliseconds in the anesthetized animal.

FIG. 7. Electrical activity of the left Rolandic region five weeks after an irritative lesion was produced in the precentral cortex by the injection of alumina cream. The electrodes are arrayed in two lines of three electrodes, with points 1, 3, and 5 lying laterally and points 2, 4, and 6 lying 5 mm. medially. Points 1 to 4 are on the precentral cortex, points 5 and 6 on the postcentral cortex. Seizure activity is present continually in the precentral gyrus, often accompanied by clonic movements of the contralateral leg. This seizure activity is best seen with the eyes closed and is momentarily blocked with opening of the eyes. Note also the absence of the fast activity seen in the normal animal.

based on electrical activity is only roughly approximate and, with the crudities of the present technic, it is unlikely that the more minute cytoarchitectonic differences which Kornmuller[3] reported could be recognized, especially when individual differences are taken into account. On the other hand, no two cortical points separated by even a few millimeters ever show identical electrical activity. Differences related to the most minute subdivisions of cortical fields may indeed exist if the relevant criteria can be detected and explicitly stated.

The electrocorticogram of the Rolandic region is particularly distinctive during the onset of sleep when the postcentral and central scalp leads show maximal high-voltage slow waves. As the sleep pattern spreads to the precentral region, a phase reversal is often seen which is similar to the pattern and distribution shown in man by Brazier.[12]

Blocking of rhythmic fast activity with movement has been previously described in man[7] and monkey[4] under local anesthesia. The present study also indicates that there is an induced 50 to 80 per second activity which accompanies the "blocking" of some rhythmic activity at the onset of movement in the unexposed brain. Our findings are in agreement with previous studies in noting the maximal electrocorticographic change in the precentral region but also present in the postcentral gyrus. This induced fast activity also distinguishes the cortical response with movement from the "alerting response" which can be induced by tactile, visual, or auditory stimuli. With alerting, one only sees a general reduction of rhythmic activity with no apparent areal maximum in the Rolandic cortex.

Whether the induced 50 to 80 per second activity is due to the electrical discharge of neurons concerned with efferent cortical processes or to proprioceptive afferents to the cortex cannot be determined from these experiments. However, since it is clear that group I muscle afferents do not activate the cerebral cortex in the anesthetized animal,[13,14] we consider it more likely that these potentials are concerned with efferent discharges. This view is supported by the recent experiments of Lilly[15] which demonstrated that movements can be elicited with electrical stimulation of any part of the Rolandic cortex in the unanesthetized animal, but with the lowest thresholds anterior to the central fissure.

The tactile evoked potential recorded from the postcentral gyrus has been studied in detail in the anesthetized and unanesthetized (ether release) monkey by Marshall, Woolsey, and Bard.[16] Our experiments differ because of the absence of pharmacologic or surgical effects and confirm the earlier study with respect to precision of somatotropic localization, relative absence of precentral responses, and the prolongation of onset latency of the evoked response with deepening anesthesia.

These experiments in the normal animal support previous findings in the anesthetized animal and man indicating that the precentral gyrus is concerned with efferent function. There is also evidence for a precentral afferent projection in man and monkey.[17] However, the central fissure forms a border dividing the maximal distribution of efferents and afferents, whether determined by anatomic, electrical, or ablation technics. From the present experiments, it is concluded that it is perhaps best to regard the fissure of Rolando as an approximate boundary in a continuous gradient of electrical activity, whether it be "spontaneous" or "evoked."

SUMMARY

The electrical activity of the Rolandic region was studied in six unanesthetized monkeys with implanted electrodes. A rhythmic activity of 25 to 30 per second and semirhythmic activity of up to 45 per second were recorded maximally in front of the central fissure. Postcentral electrical activity was predominantly slower and consisted primarily of irregular complex three to eight per second activity and occasional small bursts of eight per second alpha activity. The postcentral pattern predominated in scalp recordings.

The high-voltage slow waves appearing with drowsiness were first observed in the postcentral cortex but later appeared in the precentral cortex, replacing the usual fast pattern. During sleep 15 to 18 per second spindles appeared predominantly in the precentral cortex.

During movement of the appropriate portion of the contralateral extremity there was a blocking of the usual rhythmic Rolandic activity accompanied by the appearance of low voltage 50 to 80 per second activity of about one second duration. This fast activity appeared maximally just anterior to the central fissure, but can be recorded in all Rolandic leads. The present electromyographic technic is not adequate to determine time relation of this activity to movement, but reasons are presented favoring the view that the fast activity is a manifestation of efferent discharge. Evi-

dence is adduced to prove that this response is not due to muscle artifact or irritative effects.

Tactile stimulation elicited an evoked response only in the contralateral postcentral gyrus. Under anesthesia the latency of the evoked response was prolonged.

It is concluded that the central fissure can be regarded as an approximate boundary in a continuous gradient of spontaneous and evoked electrical activity. Although it is recognized that both precentral and postcentral cortices yield electrical manifestations of afferent and efferent processes, the distribution of these processes is quantitatively different.

The authors wish to express their thanks to Mrs. Phyllis Porter and Miss Rosa Anglas for their technical assistance, and to Dr. Jose M. R. Delgado for his helpful suggestions. His recent paper,[18] appearing as this manuscript is completed, reports inhibition of electrical activity in motor cortex (man) with voluntary movement and increased activity in these regions with sound stimulation.

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■ A transverse section of one of the anterior pyramids of the medulla oblongata in any part of its course annihilates all power of voluntary movement in the muscles behind the section on the opposite side of the body; and thus it is plain, not only that each pyramid contains very many, if not all, the conductors concerned in carrying the orders of the will to the muscles of the opposite side of the body, but also that the conductors which are collected in one pyramid decussate with those collected in the other pyramid at the lower and not at the upper boundaries of the pyramids. If anaesthesia be the result of cutting across the anterior pyramids of the medulla oblongata, its amount is too small to be unequivocal; and, in a word, all the evidence, old and new, goes to show that these bodies are composed of conductors concerned in voluntary motion without any admixture of sensory conductors.—C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

SYMPOSIUM OF INQUIRY

The Pyramidal Tract

A. M. Lassek, M.D., Clinton N. Woolsey, M.D., A. Earl Walker, M.D., and Benjamin Boshes, M.D.
—Moderator: Augustus S. Rose, M.D.

MODERATOR: The research committee of the American Academy of Neurology is pleased to present the second Symposium of Inquiry, for which the subject is the pyramidal tract. It is our earnest hope that this discussion will stimulate new ideas and motivate many of you to undertake or to expand research into the form or function of this important part of the central nervous system.

The pyramidal tract is the one portion of the central nervous system with which we all have a pleasant sense of familiarity. From the early years in medical school, we learned to equate the pyramidal tract and the upper motor neuron and, with clinical teaching, we quickly accepted the dictum that hyperactive tendon reflexes and the sign of Babinski are indicators of interruption in function of the pyramidal tract. Although these basic teachings should not be thought of as wrong, they are woefully inadequate. Much study has been done in recent years, and I believe, as our speakers summarize and challenge accepted knowledge, you will agree that there is as yet much to be learned about the pyramidal tract. The first speaker is Dr. A. M. Lassek, professor of anatomy at Boston University School of Medicine. Dr. Lassek, is probably more familiar with the pyramidal fibers than any man alive.

DR. A. M. LASSEK: The pyramidal tract has certain anatomic considerations which differentiate it from any other bundle in the central nervous system. It was the first discovered tract within the brain and spinal cord of man, having been put on the neurologic map by a German investigator, Ludwig Türck, in 1851; since that time there has been very little change in the general concept that the fasciculus is concerned with the important physiology of voluntary motion. Besides being the first observed tract, it has a known origin from the Betz cells, the largest in the cerebral cortex; it has the longest vertical course, the largest square area, and the greatest number of variable-size fibers. In its descent, it is an in-and-out tract, by the fact that it comes to the surface in the region of the basis pedunculi, in the medulla, and also in the lower part of the spinal cord. It is also one of the most recent nervous pathways to be added to the central nervous system, phylogenetically speaking, since it is present only in mammals. By contrast, it is one of the last to develop ontogenetically, requiring about two years for its maturation.

The first question I would like to raise regarding this individual part of the nervous system is in respect to its origin. What constitutes the source of all the fibers within the pyramidal tract? We might paraphrase this and ask: Do the so-called Betz cells constitute the sole source of all the fibers? These cells have been very much in the limelight since about 1874 when they were first discovered and described by Vladimir Betz, a Russian physiologist. Although they have been called "giant" pyramidal cells, I think it is difficult to give an exact definition of them, because the question arises as to what magnitude merits the classification of this term. In respect to location, they occupy a restricted part of the cerebral cortex, being located in the fifth layer of "area four" which forms only about 2.8 per cent of the entire cerebral cortex. An enumeration of these elements was first performed by Campbell in 1905; using his own standards of classification, he counted 25,000. This value, by comparison with the total population of cerebral cells, constitutes a small proportion, because it has been estimated that there are anywhere from 12 to 15 billion therein. The second count on the Betz cells, which was made in 1939 by Lassek employing different criteria, indicates that there might be around 35,000. If we descend from the level of the

Presented before the eighth annual meeting of the American Academy of Neurology, St. Louis, Missouri, April 26, 1956.

motor cortex, where these conspicuous cells reside, and examine the human pyramids below at a midolivary level following the application of one of the refined silver stains, such as the protargol method, an interesting and informative picture is presented. This investigative method reveals that there are myriads of axons at this particular level, at least a million, which is relatively large as far as nerves or tracts are concerned in man. In addition, it is possible to obtain a spectrum of diameters of these fibers by using a myelin sheath stain; measurements have shown that small ones predominate. About 90 per cent of them range between 1 and 4 microns, another 8 per cent between 5 and 10 microns, and less than 2 per cent are between 11 and 22 microns. On the basis of comparison, therefore, there is a considerable disparity between the number of Betz cells (about 30,000) and pyramidal fibers (about one million). It also seems logical to assume that large cells of the caliber of the Betz type would not give origin to the very minute fibers which predominate in the pyramidal tract. Other research of a similar nature on lower representative mammals uniformly shows great disparities between Betz cells and pyramidal tract fibers.

Since these numerical investigations, there have been other anatomic experiments performed on subhumans, particularly the monkey, to localize the possible cells of origin of the pyramidal bundle. In general, it has been found that, when the Betz cell area is destroyed, very few of the fibers disappear below. This was the finding of Häggquist, Lassek, and Mettler. The results of other similar approaches show the following on the monkey: The Marchi method indicates that there are fibers arising from the premotor, the motor, and the parietal cortex. The retrograde degenerative findings also do not harmonize with the Betz cell concept, that is, that they give sole origin to all the fibers of the pyramidal tract.

If we drop down another level in the phylogenetic scale to the cat, the recent work of Walberg and Brodal suggests that fibers descend from the temporal and occipital lobes, in addition to the frontal and parietal lobes, to lower centers via the pyramidal tract. This completes the cycle as far as the origin of the pyramidal tract is concerned, all four lobes of the brain having been implicated in various animals. It seems highly improbable, therefore, that the Betz cells contribute much more than a minor share of the total number of fibers belonging to the pyramidal tract.

The second question that I would like to raise is: What are the possible anatomic connections which make the pyramidal tract work? There must be some that are concerned with initiating, directing, and braking the impulses coursing over the pyramidal tract. By braking, I mean inhibiting or dissipating the efferent flow, signaling accomplishment. For many years certain of the British neurologists have been concerned with this question. Sherrington (1895) was the first to advance the view that the pyramidal tract is comprised of internuncial neurons which conduct under the influence of afferent nervous impulses acting upon their cells of origin. Bartlett, Bastian, Walshe, Gooddy, and Adrian likewise have felt that it is the afferent system, in association with its different receptors, which is concerned with this particular phase of pyramidal activity.

The third question which I would like to raise is: What is the possible function of the many fine fibers which are present within the pyramidal tract of all mammals? They are very small. About 50 per cent of them are of the caliber of 1 micron in diameter. We may suspect that these fibers are visceral from the physiologic viewpoint. There have already been some basic electrophysiologic investigations which take into consideration these relatively miniature neurons. The results indicate that they may subserve an autonomic function. This subject infringes on Dr. Woolsey's discussion, so I won't elaborate on it. But, if these numerous small fibers are concerned with an autonomic role, then we have to change our physiologic concept of the pyramidal tract entirely, because, quantitatively speaking, they constitute a major proportion of it.

The fourth question is a challenging and a radical one. This is in respect to the possible presence of ascending fibers within the pyramidal bundle. For more than a hundred years, we have regarded the pyramidal tract as being comprised entirely of descending fibers. Some of the research supporting this view has been of an anatomic basis. Brodal and Walberg, using both silver and Marchi stains, have found fibers which arise somewhere within the spinal cord of the cat and course rostrally within the pyramidal tract. They also described similar neurons originating from the nucleus gracilis and cuneatus. More recently, Nathan and Smith reported fibers passing up in the pyramidal tract in man; they based their conclusions on studies made after section of the lateral spinothalamic tract in 43 cases. In these operations, the anterior part of the pyramidal

tract was nicked unintentionally; they were able to trace degenerated fibers upward in the motor bundle under consideration and were surprised at the number present; they noticed that many were of large caliber. Because of its importance and significance, further experiments will undoubtedly be performed to clarify this question.

The fifth point I would like to raise about the pyramidal bundle is in respect to its phylogenesis. Under this topic, there is one thing that stands out, that is, the variability of the tract as we go down the mammalian scale. One constant feature is that in all such animals it courses through the pyramid. It varies as to its extent down the spinal cord and may terminate anywhere throughout its entire length. In this portion, it may occupy any funiculus, the anterior, posterior, or lateral, and it differs in the number of fibers present. From the evolutionary viewpoint, it begins as a tiny tract with very small fibers; as we go up the phylogenetic scale, there are certain predestined ones which become larger and larger and these reach their maximum in man. However, the fact is that in all animals studied they form only a small part of the total number. It is very difficult, if not impossible, to determine what the over-all phylogenetic function of this tract may be, when comparing microscopic anatomy with physiology. There are some animals, for instance, that have poorly skilled motor functions, some of the hoofed ungulates for instance, which have very well developed tracts numerically.

The sixth and last point that I would like to mention revolves around where the pyramidal fasciculus stands in the hierarchy of tracts which influence the anterior horn cells. I think that, before long, the trend in the research field of motor mechanism will be in the direction of trying to learn more of the changes which occur in its evolution, its ontogenesis in man, correlating structure with physiology in both. Also of interest is the role of the afferent system in respect to initiating and dominating the efferent cells functioning in movement. As for the pyramidal tract as an isolated unit, it is expendable in lower mammals and may be in man also, if lost very early in life. It may be that, from the broad viewpoint, the afferent system may come first in the phenomenon of training the motor component to function during ontogenetic development, that it may dominate and control it throughout life, and finally that it may be the vital factor in restitution of function following injury to efferent units, including the pyramidal tract.

MODERATOR: Thank you, Dr. Lassek. It is evident that there are still many areas yet to be determined in the morphology of the pyramidal system and there are many inferences to be drawn concerning function. It is appropriate for our second speaker to present the physiology of the pyramidal tract. Dr. Clinton N. Woolsey, professor of neurophysiology at the University of Wisconsin Medical School, has been working in this field for many years and is an eminent authority on the motor cortex in animals.

DR. CLINTON N. WOOLSEY: The role of the cerebral cortex in the control of motor function has long been subject of both clinical and experimental studies. After the first successful cortical stimulation experiments of Fritsch and Hitzig, the work of Ferrier and others rapidly led to the view that the "motor area" consists not only of the precentral rolandic region, but also of most of the cortex of the parietal lobe. This view prevailed very generally until the work of Leyton and Sherrington in 1917 established that in the precentral gyrus there is an area of low threshold to electrical stimulation. This led to the view that the postcentral region is not a part of the "motor cortex." The effects of stimulating the parietal cortex were then explained as due to activation of the precentral region through corticocortical connections or to spread of stimulating current to the low threshold precentral system. Foerster, following the work of the Vogts, analyzed cortical motor responses of the pre- and postcentral regions in terms of pyramidal and extrapyramidal systems and held that localized effects of postcentral stimulations could be obtained only when the pyramidal tract, thought to originate only from the precentral gyrus, was intact. The less specific synergic movements which survived pyramidal tract injury were termed extrapyramidal.

A somewhat similar view was expressed by Hines in 1943 in her review on motor systems of the brain. Her conclusion was supported by her own work and that of Tower on animals in which the medullary pyramids had been cut. In these experiments, the isolated or more detailed movements produced by stimulating the precentral region in animals with intact pyramids were abolished and only adversive and synergic movements of trunk and limbs remained, even in animals that had survived pyramidal section for some time. Dr. Lassek has just told us that there are anatomic reasons for supposing that there are other regions

of the cortex than the precentral gyrus which contribute fibers to the corticospinal tract. Recently Penfield has written: "It may well be that the major representation of movement is in the ganglionic clusters of area 4, and that stimulation of the Rolandic cortex anterior and posterior to it activates those clusters, but there is evidence that the postcentral gyrus also sends a few efferent motor fibers down to bulbospinal centers." Levin and Bradford in retrograde studies found that 20 per cent of cortical cells identifiable as affected by hemisection of the cord were in the parietal cortex. Peele reported Marchi degenerations in the pyramid after lesions limited to parietal cortex, and antidromic studies by Woolsey and Chang indicated origin of pyramidal tract fibers both from the precental agranular cortex and from the entire parietal lobe.

In recent years our laboratory has reexamined the question of cortical motor centers in the monkey and has defined anew the pattern of localization in the precentral motor area, establishing boundaries somewhat different from those previously accepted and adding significantly different and new information concerning the intraareal organization of this motor field. These results suggest that it may be well to look again at the human cortex with these new features in mind.

The supplementary motor area, which Penfield and Welch described for man and later for monkey, has also been charted in detail in the macaque. Thus, in the frontal lobe there are two complete representations for the contralateral somatic musculature.

The boundaries of our precentral motor area and of the supplementary motor area do not coincide precisely with anatomic or functional boundaries of frontal motor areas as defined by earlier workers. Our *precentral motor area* is very similar in extent to Brodmann's original definition of area 4 in the monkey. In the Vogts' parcellation, it includes area 4a, 4b, 4c, and most if not all of their 6aα on the dorsolateral surface. The medial aspect of the hemisphere of the precentral motor area includes their area 4a and that part of area 6aα from which they obtained movements of vertebral column, tail, and anus. In the terminology of von Bonin and Bailey, our precentral motor area consists of FA, FBA, and a part of FB on the outer aspect of the hemisphere. On the medial wall, most of FA falls within the precentral motor area, but the exact extent of this field does not appear to agree too well with the limits of our precentral area.

The *supplementary motor area* lies within Brodmann's area 6, but it does not include those parts of area 6 on the dorsal and lateral aspects of the hemisphere. In Bucy's monograph, von Bonin uses the term precentral motor cortex to include Brodmann's areas 4, 6, and 44. His usage of the term is, therefore, not equivalent to ours. The Yale workers used the terminology of the Vogts; their "motor cortex" is less extensive than our precentral motor area and their "premotor" area includes the rostral part of our precentral motor area, the supplementary motor area, and Vogts' areas 6aα and 6aβ. These various terminologies are not interchangeable.

The question of the motor functions of the parietal lobe has also been under review. In 1943 Kennard and McCulloch studied the electrical excitability of the postcentral gyrus sometime after removal of areas 4 and 6 from infant monkeys and found that it was still possible to produce focal movements similar to those normally elicitable from the precentral gyrus. Recently we have mapped in detail the motor effects of stimulating the postcentral gyrus of adult animals from which the precentral and supplementary motor areas had been removed months previously. The motor localization pattern of the postcentral gyrus was shown to parallel the sensory input pattern, even in the absence of the motor centers of both frontal lobes. In 1948, Sugar, Chusid, and French described a "second" motor area in the monkey in the parietal operculum near the "second" somatic sensory area. Study of the squirrel monkey has demonstrated that this "second" motor and the "second" sensory area are not separate areas but correspond in situation and in somatotopic organization. Two motor outflows, therefore, exist in the parietal lobe. Thus, the rolandic motor field is at least as extensive as it was thought to be at the turn of the century, but it can now be considered as composed of four functionally distinguishable components. It appears that all four of these areas contribute fibers to the pyramidal tract. It is possible that all four in addition make nonpyramidal connections to the brainstem and cord. New studies to examine the roles of these several motor systems in motor function have been made and some of the results have been reported.

In closing, I should like to draw the attention of this audience to some facts which are not generally known or appreciated concerning the distribution of degenerating pyramidal tract fibers in the spinal cord of the monkey,

although they were reported many years ago by Sherrington and were noted recently by Glees and Cole. They are illustrated in detail by Barnard and Woolsey, from whose paper these slides were taken. The principal features to which I would draw your attention in these Marchi sections, made 41 days after complete removal of the precentral motor area of one hemisphere, are the appearance of a heavy lamina of corticospinal fibers superficial to the dorsospinocerebellar tract in the cervical segments. The fibers can be followed to this position from the pyramidal decussation in C_1. In the lower cervical segments, this superficial lamina becomes fused with the more centrally placed portion of the lateral corticospinal tract, so that the whole tract extends outward as a solid mass from the gray matter of the dorsal horn to the surface of the cord. The superficial position is still distinguishable by the fact that it extends as a broad mass well below the level of the central canal in the lateral column of the cord.

It would be of great interest to know whether the lateral corticospinal tract in man shows these features, both for theoretical and for practical reasons in connection with tractotomy operations. The question might be answered by Marchi studies on material coming to autopsy within two months after extensive cortical, capsular, or peduncular lesions.

MODERATOR: Dr. Woolsey, you have given us a great deal to think about and I'm afraid it is going to be difficult to rearrange some of our old concepts. I expect you will have many questions from the panel and audience. Our third speaker is Dr. A. Earl Walker, professor of neurologic surgery at Johns Hopkins School of Medicine. Dr. Walker has made many contributions to neurologic knowledge – in morphology and physiology, as well as in clinical neurology and neurosurgery.

DR. A. EARL WALKER: Almost from the time of its origin, the name "pyramidal tract" has been criticized as ambiguous and misleading. In this discussion the term will be used to refer to those fibers which pass through the medullary pyramid. It is recognized that this definition would alienate those neurosurgeons who speak of "spinal pyramidotomy" when they refer to sections of the lateral column of the spinal cord. Moreover, by confining the discussion to the fibers passing through the pyramids, the surgeon must admit that he has nothing to contribute to the subject, since in man the medullary pyramids are not accessible to the scalpel or to the stimulating electrode, and rostrad and caudad, its fibers are intermingled with those of many other systems. Accordingly, if this presentation were to be limited strictly to the subject, it would be finished at this point. However, if the neurosurgeon be allowed the same liberties as his neurophysiologic, neurologic, and neuroanatomic colleagues' interpretation of this subject, some interesting data may be presented for discussion.

The surgeon has placed his stimulating electrodes or wielded his scalpel upon almost all parts of the pyramid tract, from its origin in the cerebral cortex to its termination in the spinal cord. This surgical interest in the pyramidal tract has been based upon two theses: 1) that this system at its origin was to some extent at least concerned in focal motor epilepsy, and 2) that, although involuntary movements are initiated by dysfunction of such subcortical centers as the cerebellum, substantia nigra, thalamus, caudate nucleus, putamen, and globus pallidus, the integrity of the pyramidal tract or some intimately related fiber system is essential for the development of dyskinesia. Both of these hypotheses are not too well founded and may not stand the test of time, but they have been the basis of a great deal of surgical therapy for both epilepsy and involuntary movements. In the neurosurgeon's mind, the pyramidal tract has been generally equated with those fibers which carry the impulses, induced by his stimulating electrode, that give rise to a contraction of the somatic musculature. True, lip service is always paid to the possible participation of other fiber systems, but the pyramidal tract has been tacitly assumed to be the most important motor tract. This hypothesis seemed to gain confirmation when the cortical area, which gave motor responses upon electrical stimulation with minimal thresholds, was shown to be that from which much of the tract originated. The responses and their somatotopic representation in the central gyri have been so well described by Horsley, Foerster, Krause, and more recently by Penfield and his associates that no time need be devoted to discussing this subject. That these motor responses are mediated solely by corticospinal neurons is a moot question. In man, no comparison has been possible of the movements elicited by electrical stimulation of the motor cortex of the normal and apyramidal individual, that is, the individual with the pyramids sectioned so as to indicate which types of movement were due to impulses passing along pyramidal and nonpyramidal fibers. As Marion Hines has stated, the use of

an electric current with supraliminal stimuli is adequate to excite many fibers other than pyramidal. If one may translate to man the findings of Tower following medullary pyramidotomy in the monkey, one might state that the extrapyramidal fibers may give rise to stereotyped synergies and to various inhibitory phenomena. This has led Fulton to state that "isolated volitional movements thus depend upon the integrity of area 4 and the pyramidal tract." Certainly, however, it is reasonable to believe that the stimulating electrode applied to the precentral gyrus excites neurons of both pyramidal and extrapyramidal fiber systems and that the results of this excitation may be due to a combination or multiplicity of responses by these two systems. Much thought has been expended in the discussion of the type of motor representation within the cerebral cortex. Although Hughlings Jackson stated that "nervous centers know nothing of muscles, they only know of movement" and Sherrington concluded that "movements, not muscles, were represented in the motor cortex," much work has been carried out on experimental animals to indicate that contraction of muscles or portions of muscles may be produced by stimulation of the precentral cortex. Perhaps this argument is more philosophic than practical, since it seems probable that one corticospinal fiber will influence more than one cell, either of the zona intermedia at the base of the posterior horn or of the anterior horn. Each anterior horn cell affects a number of muscle fibers. Moreover, it would seem probable that, under normal operating circumstances, not one but many cells of origin of pyramidal fibers are activated and that the resultant phenomena reflect their influence upon rather complex spinal cord units.

Perhaps some comment should be made upon the inhibitory effects of cortical stimulation, although these responses are generally considered to be mediated by extrapyramidal rather than pyramidal fibers. In man, there is no doubt that inhibition may be obtained by stimulation of the precentral gyrus and adjacent motor cortex. This has been well documented by Foerster, Penfield, Bucy, and many other surgeons. But there is no evidence that a suppressor band or system of bands exists, as described by Dusser de Barenne and elaborated by McCulloch. True, involuntary movements may be occasionally arrested by stimulation of the precentral convolutions, but the area giving rise to such inhibition does not form a strip anterior to area 4. Rarely, the reverse, namely facilitation of involuntary movements, may be induced by cortical excitation, as in Bucy's first case.

The neurosurgeon has removed both motor and premotor areas, individually and together, for the relief of both epilepsy and involuntary movements. Whether the beneficial results are due to the removal of a considerable part of the origin of the pyramidal tract is an open question. In focal motor epilepsy, the results following this procedure are not as satisfactory as those obtained by removal of the temporal lobe for psychomotor fits. At best, not more than 20 to 25 per cent of patients are relieved of their attacks. In cases of parkinsonian-like tremor, removal of the precentral convolution will eliminate the shaking, substituting for it a paralysis of the previously involved part. For athetosis, a more extensive precentral and premotor (area 6) ablation is necessary. In dystonics, even extensive extirpations do not modify the movements, which would suggest that the pyramidal tract is not essential for their genesis.

The neurologic deficit resulting from the cortical resection of the precentral origin of the pyramidal tract is so well known that further description is unnecessary. Marion Hines has described the spastic hemiparesis which results from ablation of the precentral convolution. Perhaps, however, some comment on the effect of age upon the neurologic deficit is pertinent. If one examines patients who have had hemispherectomies for brain tumors originating in adult life, one notes that, although the patient is able to walk without aid, the gait is typically that of a spastic hemiplegic, with few movements of the toes or ankle. In the upper extremity, voluntary individual movement of the fingers and wrist is absent and the ability to increase the spastic flexion of the fingers on command is usually absent.

Patients suffering from infantile hemiplegia have a degree of hemiparesis which does not reach the extreme state found in adults with acquired hemiplegia. These young people usually have considerable motility of the shoulder joint, some ability to flex and extend the elbow, and often feeble and awkward movements of the wrists and fingers of such a range that they can hold objects in the fingers. Walking is possible in spite of the spastic hemiparesis; the hip and knee can be flexed and extended and even the ankle and toes may only be moved as a unit. Following hemispherectomy, which none will deny eliminates the cortical origin of the pyramidal tract, movements of

the previously hemiparetic side are rarely affected. McKissock reported that two of his 18 patients had some impairment of movements of the contralateral side, but most other surgeons do not consider that there is any decrease in strength. My personal experience would be in accord with this; in fact, the mother of one patient stated that even the morning after operation her son was able to use his extremities, both the upper and lower, as well as he ever had been in his life. This difference in the state of paralysis in young individuals with an infantile hemiplegia and in older individuals with acquired hemiplegia is generally assumed to be the result of the development of ipsilateral innervation of the extremities and perhaps some innervation from basal structures on the contralateral side. Bates has emphasized the importance of ipsilateral innervation by demonstrating that stimulation of the mesial aspect of the ipsilateral hemisphere will induce movements of the ipsilateral extremities almost to the extent which can be brought out volitionally. Apropos of the apparent increased ipsilateral control of voluntary movements in these infantile hemiplegias are the observations of many authors of a compensatory hypertrophy of the ipsilateral pyramidal tract. Von Monakow, Déjerine, and numerous other European authors have commented upon this condition. Verhaart believed that the hypertrophy was not due to an increase in the number of fibers but simply the result of an abnormally large number of thick fibers, for he found that there were more fibers in excess of 3 micra than usual, whereas the number of fibers below that size was well within normal limits. This is an interesting observation, although the significance of the large fibers in the pyramidal tract is not apparent at this time. In his early attempts to section the ansa lenticularis for involuntary movement, Meyers removed the head of the caudate nucleus and cut the anterior limb of the internal capsule. To Jefferson Browder, this latter lesion seemed the important and therapeutic part of the operation. Accordingly he carried out this procedure under local anesthesia in a series of parkinsonian patients. As the internal capsule was being cut, the patient's tremor stopped, but Browder found that for permanent relief it was necessary to continue cutting the capsule until the patient was just barely able to flex his fingers. Stopping at this point, Browder found that the patient regained practically normal power in the hand within a few weeks, although he considered that he had cut a large part of the corticospinal tract. This marked recovery after such a lesion is noteworthy in view of the further discussion of the pyramidal tract.

In the last ten years the neurologic surgeon has become interested in interruption of corticospinal pathways at the cerebral peduncle for the relief of involuntary movements. This portion of the pyramidal tract was selected because the fibers of the pyramidal tract are fairly compactly arranged in the cerebral peduncle, relatively accessible to surgical intervention, and topographically oriented so that they can be cut selectively with little danger or damage to other important systems. A further therapeutic advantage was envisioned, namely, that since a considerable number of extrapyramidal fibers might not be damaged by a lesion of the cerebral peduncle, the motor power might be preserved at least to some degree. In man the cerebral peduncle is a prominent structure at the base of the brain, between 1.7 and 2 cm. in width, through which run tracts descending from the cerebral cortex to brainstem and spinal centers. The precise definition and topographic arrangement of these tracts in the peduncle is not known, but a frontopontine bundle of fibers is known to course through the medial, and a temporopontine tract through the lateral third of the crus cerebri. Stimulation (60 cycle sine wave; a 1-2 volts) of this structure in man gives rise to no movements as the electrodes are moved from the lateral to the medial aspect of the peduncle until the middle third is reached, when flexor movements of the legs are noted. Further medially, arm movements, usually flexion of the forearm and hand, may be produced. At times the movements of both the arm and leg occur and isolated responses cannot be obtained. Stimulation of the most medial portion of the peduncle has not induced a motor response. It must be admitted that, because of the depth of the peduncle, a careful analysis of the results of stimulation of the cerebral peduncle has not yet been made.

A variety of operative procedures have been carried out upon the cerebral peduncle, usually with the intent of interrupting the corticospinal tract to a greater or lesser extent. However, section of the cerebral peduncle at any part unquestionably interrupts many other as yet poorly known tracts. My personal experience with this technic is based upon some ten cases in which section has been made of the peduncle for the treatment of involuntary movements. The sections in these cases have

been made of the lateral half to four-fifths of the peduncle or only of that portion of the peduncle which upon stimulation gave rise to movements of the extremity involved by the tremor. The cuts in these cases were made 7 mm. deep, which should carry the incision to the substantia nigra. However, the precise position of these incisions has not been verified since no patient has died. Other surgeons have made smaller incisions, Guiot and Pecker making a 3 mm. deep cut, presumably across the entire face of the cerebral peduncle. Meyers has sectioned the medial third of the peduncle and more recently the middle third; Bucy has also cut the middle third in one patient. From these experiences one interesting fact has developed, namely that the amount of paresis which has followed the operation has been much less than the operator had expected from the extensive section of the corticospinal tract. This was particularly true in my first case, in which a section was made of the lateral two-thirds of the cerebral peduncle for hemiballismus. This patient had a very transient weakness of the right extremities which cleared up almost completely within a few months. Both Meyers and Bucy have commented upon the fact that the weakness was not commensurate with the presumed damage to the corticospinal tract. In fact, on the basis of this observation, Russell Meyers has suggested that the corticospinal tract does not subserve ordinary volitional movements. However, before this conclusion can be drawn, one must establish the fact that the corticospinal tract has actually been sectioned by these pedunculotomies. In most of the patients operated upon today, the pathologic condition had existed for many years, in some cases from birth, so that the corticospinal tract might be very small and displaced within the cerebral peduncle. Accordingly, an interruption of the middle third of the cerebral peduncle might not interrupt the fibers of this tract. I must confess that in these cases in which I have stimulated the peduncle before sectioning the corticospinal tract, placing my incision at the point where excitation produced movement of the extremities, there has been an appreciable and lasting hemiparesis, although not necessarily a complete paralysis. Excitation has been made rostral to the incision in the peduncle until the peripheral responses are practically abolished. In such cases the resultant hemiparesis is mild to moderate and usually long-lasting.

The neurosurgeon has a special interest in the corticospinal tract in the cervical cord because of two considerations: first, at this level the pyramidal tract is relatively accessible to surgical section for the relief of involuntary movements, and second, the proximity of the corticospinal tract to the lateral spinothalamic tract which the surgeon wishes to section for the relief of intractable pain. Unfortunately no careful study in man has been reported on the effects of stimulation of the lateral column of the spinal cord.

Spinal pyramidotomy, introduced by Tracy Putnam for the relief of involuntary movements, has been carried out by a considerable number of investigators. The results of such sections seem to be fairly well in agreement. In the first place, the tremor is abolished for a longer or shorter period. Secondly, there is paralysis of the body below the site of the incision, usually made in the middle or upper cervical region. This weakness is said to decrease gradually so that the residual weakness is minimal. Dorsiflexion of the ankle seems to be the weakest movement in the leg; there is considerable impairment of movements of the upper extremity and hand. Increased reflexes and a positive Babinski are the rule in such cases. If the anterior columns are cut, as Ebin did, the residual weakness is greater.

For many years the neurosurgeon has noted paresis of the legs following bilateral cordotomy in practically one-third of cases and following unilateral cordotomy much less frequently. Grant reported postoperative paresis in 17 per cent of bilateral and 6 per cent of unilateral thoracic cordotomies, and White and associates 8 per cent. Hyndman emphasized that this paresis was usually flaccid and accompanied by a loss of extensor tonus. Although neurosurgeons have generally considered this complicating weakness the result of concomitant involvement of the lateral pyramidal tract, complete section of the anterior half of the spinal column produced a flaccid paralysis and a loss of extensor tonus persisting for a longer time than a section of the lateral pyramidal tract alone. In analyzing the material at the Serafimerlasarettet, Bernhardt and co-workers found that in bilateral cordotomy a paraparesis occurred in 13 cases and a monoparesis in two. Since the frequency of postoperative paresis after unilateral cordotomy is significantly lower than that after bilateral section, they argued that the paresis was not the result of pyramidal tract injury but the interruption of a facilitory tract in the anterior half of the spinal cord which was both ipsilateral and

contralateral. To demonstrate this they sectioned the anterior quadrant of the macaque spinal cord and found upon electrical stimulation of the motor cortex that no response could be obtained from the peripheral nerves. Histologic examination of their material did not demonstrate involvement of the corticospinal tract. They further pointed out that Ebin's technic of lateral pyramidotomy produces a much greater paresis than the pyramidotomy originally employed by Putnam and later by Oliver and Sjöqvist. Thus, the functioning of the pyramidal tract is dependent upon the integrity of certain other facilitory systems. In man the pyramidal tract still presents many problems, both anatomic and physiologic. From this survey of our present concepts of the tract it is obvious that the cortical origin of the fiber system, if damaged, gives rise to a much more severe and lasting paresis than the interruption of the fibers at any other point in its course. The significance of this is not entirely clear. Does the human precentral cortex contain cells giving rise to both "pyramidal" and "extrapyramidal" fibers which are capable of effective activation of the spinal motor units? This is possible, for the organization of the motor system in man may be quite different from that of the monkey, just as the latter differs from the cat. Certainly a precise somatotopic cortical representation would not fit with the lack of paresis following lesions of the pyramidal tract. With a clear definition of the problem, these questions are capable of solution, even in man. Future research in this system may well elucidate some of the mechanisms of the pyramidal tract and indicate which of our present conceptions are correct and which are in need of revision.

MODERATOR: Our last speaker, Dr. Benjamin Boshes, is professor of neurology at Northwestern University School of Medicine. He will discuss the pyramidal system from the viewpoint of the clinical neurologist and teacher.

DR. BENJAMIN L. BOSHES: Tonight we must attack the neurologic temple, the sanctuary of the upper motor neuron lesion due to a lesion of the pyramidal tract. This is a most sacred concept. We teach it to our medical students from the freshman year on, drill it into our residents, and test the Board candidate to see if he has incorporated the principles into his neurologic formulations.

Let us examine the truths in the tenets of such a lesion which produces weakness to paralysis, spasticity, increased deep reflexes, diminished to absent superficial reflexes, pathologic reflexes, no atrophy, and no reaction of degeneration.

Weakness. Are the limbs always weak? Usually, but sometimes not. Sometimes the lower limb is prop-like and can be unlocked only by a Marie-Foix maneuver, after which we see a clasp-knife withdrawal. In the upper limb the flexed forearm is often very strong, resisting extension. The patient can carry heavy loads. He is not bothered by the weakness. He says, "The limb is heavy, numb, dead, not mine." It is a sensory description. This is not entirely a matter of semantics. There is a real basis in neurophysiology. Often the chief motor deficit is loss of skilled movement, for example, in the fingers.

Spasticity. What is this? Some six years ago, Denny-Brown defined it as "an uncomplicated increase in the stretch reflex such as to give a progressive reflex response in a muscle to stretching of that muscle." H. W. Magoun and Ruth Rhines would have it otherwise. They accept the increased resistance to manipulation, but they add hyperactive deep reflexes and clonus. To Denny-Brown, clonus is an epi-phenomenon which represents a complication of spasticity. All of us have seen instances of hypotonic muscles as in subacute combined degeneration of the spinal cord where, by gentle evocation of the stretch reflex, it has been possible to elicit a sustained clonus. We have also seen severely spastic limbs after spinal cord injury where it was impossible to evoke clonus. Is the spasticity, when present, the result of removal of inhibition from the pyramidal tract? Evidence from surgical ablation of area 4 in man would suggest that only mild spasticity ensues. The arm hangs flaccidly. For a week or two following surgery, all the affected limbs are hypotonic from neural shock. The work of Marion Hines on area 4S would suggest that this anterior portion of area 4, through connections in the caudate nucleus, suppresses the mechanisms which produce spasticity. However, Russell Meyers was unable to delineate a 4S area in the unanesthetized human cortex. Magoun and Rhines discard the pyramidal tract entirely in their consideration of spasticity. They believe that the reticulospinal system possesses inhibitory and particularly excitatory divisions. Cortical, striatal, and cerebellar connections with the reticular inhibitory cells exist so that lesions involving any of these parts independently can produce spasticity. Why, however, is a proved anatomically complete transverse lesion of the cord often associated with spasticity? Here no

facilitory reticulospinal bombardment exists. Magoun and Rhines consider the facilitators from the reticular formation more important than the inhibitors. Denny-Brown, I believe, is closer to the facts when he described spasticity as a phenomenon of disequilibrium between proprioceptive reflexes and those which trigger them. The loss of the corticospinal tract destroys the balance. Fulton is inclined to agree and points out that the myelosynaptic reaction is facilitated by vestibular nuclei and reticular facilitory areas and inhibited by area 4S, the caudate nuclei, and anterior lobe of cerebellum. Spasticity, therefore, is not merely a release from the inhibition of the so-called pyramidal tract but the result of the positive action of other superiorly placed mechanisms. What ensues in the more fully recovered isolated spinal segment in man where all upper-level influences, inhibitory and facilitory, are removed, we shall take up later. This is a new chapter in physiology. But even now we may ask the question, "How important is the pyramidal tract per se in spasticity?"

Increased deep reflexes. These are seen in a chronic lesion. In an acute lesion, the reflexes do not come back for a week to ten days, after which they generally increase. In lesions of area 4, they may remain diminished. Deep reflexes are pendular following lesions of pyramids and parietal lobes (Hines).

Diminished to absent superficial reflexes. Here is an area about which we know little. Certainly in the adult this segmental, polyneuronal reflex depends on facilitation through bombardment from higher levels and the corticospinal tract seems to be the chief factor. However, in cortical lesions (area 4) the abdominal reflexes are often retained or recover, and after hemispherectomy in children, where even the caudate nucleus is removed, the abdominal reflexes return. In amyotrophic lateral sclerosis where the entire pyramidal tract may be destroyed. the abdominal reflexes may remain intact. The pyramidal tract holds no exclusive influence here. What is the mechanism of the abdominal reflex?

Pathologic reflexes. First and foremost, we have the Babinski toe sign, the most important abnormal sign in clinical neurology, presumably the most exquisite evidence of pyramidal tract involvement. However, it is seen during hypoglycemia, after certain anesthetics and drug administration, during alteration of cerebral blood flow for whatever cause, in meningitic reactions due to blood or chemicals, in edema of the brain, after epileptic seizures, and even during sleep. A tight bandage on the leg or a cold room will abolish it, a warm foot bath or scopolamine will enhance it.

A study of the history of the sign helps explain our slavish addiction to it, for here is often what happens to an eponymic symptom. When, toward the end of the nineteenth century, Babinski described the extension of the toes, especially the big toe, and then the abduction of one or more toes, later called the "sign of the fan," he stated that this "appeared to be" the result of "a perturbation in the function" of the pyramidal tract. He described finding his sign when the pyramidal tract was intact and after strychnine poisoning. Early he stated that he saw no need for an anatomic or histologic lesion to explain it. He preferred to keep his sign "in the realm of clinical observation." But the requested isolation did not last. Enthusiasm for the sign spread and, with it, transmutation of meaning. By 1899 Collier (in non-anatomically confirmed cases) reported that the sign was pathognomonic of a lesion of the pyramidal tract. "Parait etre" had become "pathognomonic" and "perturbation dans le functionnement" had become "lesion." The neurologic world followed Collier's words and even Babinski was swept up in the new interpretation. Tonight, almost 70 years later, we are asking the function of the pyramidal tract. How can we even explain Babinski's "perturbation of function" in a tract about which we know so little?

In 1955, two Englishmen, Nathan and Smith, examined the phenomenon critically. They mentioned Papez and Vanderahe's case of a man who had a proved absence of area 4 and no Babinski sign. They studied a series of patients in whom chordotomies of various types had been performed to relieve pain of malignancy. All cases were anatomically verified after death. They concluded, "There is no relation between the anatomic state of the corticospinal tracts and the form of plantar response. To regard the Babinski sign as a spinal reflex whose manifestations are prevented by the functioning of one and only one (the corticospinal tract) is an over-simple conception of neurophysiology."

This statement fascinated me. What would happen when all or essentially all the descending tracts were cut or otherwise interrupted? To test this, I asked our group at Hines Veterans Administration Hospital last week to examine 100 cases of severe spinal cord lesions, all in good condition nutritionally, all paraple-

gias-in-extension with no atrophy. No cauda or conus lesions were tested.

	AC	PC	PI	Total
Dorsiflexion, large toe only	0	7	5	12
Fanning of toes only	1	2	3	6
Withdrawal only	1	4	3	8
Dorsiflexion, large toe, and fanning	2	9	4	15
Dorsiflexion, large toe, fanning and withdrawal	0	15	18	33
Dorsiflexion, large toe, and withdrawal	2	7	12	21
Fanning and withdrawal	0	2	3	5
Total	6	46	48	100

(AC, anatomically complete; PC, physiologically complete; PI, physiologically incomplete.)

We are very vague in our concept of a Babinski toe sign and I have read any number of methods to elicit it. Shall we stroke up, down, or cross-wise? Hockey-stick pattern or transverse? Board candidates literally leave the signature of their preceptors as they excavate a patient's planta. What is one after here? The purpose is to fire a volley into the cord which will reach essentially levels L_5 and S_1. The stimulus may be touch, stroke, pinch, pluck, cold, and even stretch. One may start stroking gently at L_1, then L_2, L_3; at L_4 the big toe begins to draw up; at L_5 the toes begin to fan; at S_1 the reaction is increased and beginning withdrawal synergia starts. The elicitation must be delicate, quantitated to utilize liminal stimuli to avoid violent flexion synergias. Sometimes abducting the opposite thigh to prepare the limbs for proper positioning for reflex elicitation is sufficient to elicit a crossed dorsal flexion of the big toe. This volley goes in at L_2 and informs the examiner that it travels without check down to L_5 to elicit the dorsal response. Such information is useful; something is different in this cord. What goes on in such a system?

The Rossolimo sign is another favorite pathologic reflex. It is found in 2 to 3 per cent of purported normals. There is no clear-cut evidence that it belongs to the pyramidal system, although it is believed that the fibers which subserve it run near the pyramidal tract. Many believe it to be abnormal latent or extrapyramidal reflex released by lesions involving area 6.

The Hoffmann sign, attributed to him by his friend Curschmann who wrote it up in 1912, is a heightened stretch reflex seen often in normals and after all kinds of upper motor neuron lesions. It is nonspecific unless asymmetric.

Atrophy and reaction of degeneration. These are unusual except in the infrequent instance of isolated spinal cord segment which "dies" with attendant change in nerves and muscle—"isolation dystrophy."

Spinal shock. What role does the pyramidal tract play here? In lower forms like the cat (you are all familiar with the classical experiment of Fulton, Liddell, and Rioch), the vestibulospinal and ventral reticulospinal tracts protect the animal against this phenomenon. What causes spinal shock or diaschisis a la von Monakow? It appears that in man the spinal cord is bombarded by volleys of facilitating stimuli, from above particularly, by way of the corticospinal tract. When these are interrupted suddenly, spinal shock ensues. Chronic interruption, as in tumor, does not produce diaschisis. The events that follow depend on the year of the report. In 1890 H. Charlton Bastian reported that, after a total transverse lesion of the cord, there was a permanent loss of all reflex activities below the level of the transection. The studies of Riddoch, Holmes, Head, and Walshe in 1917 refuted Bastian's law. They described the large flexion synergias of the lower limbs, the mass reflexes. The concept evolved that the released spinal cord with predominant flexor responses which often terminated in a paraplegia-in-flexion indicated that the cord was totally transected physiologically. If the paraplegia remained in extension, this was evidence that the vestibulospinal tracts were intact and that the lesion was incomplete.

Such was the state when we, among others, began our studies during and after World War II. Patient after patient had massive flexor spasms. But were these spasms spontaneous? A case in point brings out the physiology clearly. An old man in the middle 80's was brought in for consultation because he was a nursing problem. He would not keep the covers on. He held his right leg drawn up tightly and "refused" to put it down. The physiology was simple. Gentle stroking of the right planta produced dorsiflexion of the big toe. Plucking of a midline pubic hair produced a bilateral flexion synergia, pulling the right thigh up even farther than before. It was obvious that he had a transverse cord lesion, but where? Anteflexion of his head pulled the umbilicus up 2 cm. in a clear Beevor sign, a lesion at T_{10}. The suspect T_7 vertebra was exquisitely tender, the site of a later proved compression fracture. I asked myself, "Why flexion on the right, extension on the left? Where is the right volley firing from?" The reason was quickly forthcoming. Deep between his buttocks to the right of the perineum was a hemorrhage

and later x-rays showed a well-impacted intertrochanteric fracture of the right femur. Such is the story of the so-called spontaneous spasms, the precursors of a paraplegia-in-flexion. The severity has no strict relation with completeness or incompleteness of the lesion. The problem is more closely related to good nursing care. Unilateral decubiti, fractures, and osteomyelitis produce ipsilateral flexor spasms; bilateral complications cause both limbs to draw up. Midline stimuli, calculi, infected catheters, orchitis, and epididymitis cause bilateral spasms. Good nursing care, with restoration of blood count, albumin-globulin ratio, total blood protein, and elimination of infection and irritants, enables the patient to pass through the flexor stage, sometimes as early as six months after verified anatomic section, to enter the extension state. Various reflexes involving the genitals, reflex stepping, and bicycling movements may now be elicited. Time does not permit details here, but it may be said that the higher the lesion rostrad, the more reflex activity may be elicited from the autonomic spinal cord segment. There is much to be learned here in this simplest of natural preparations, spinal man, for he has just now reached a state where our examinations are becoming meaningful. Bastian's patients did not react; Riddoch's reacted too much; then an infection stopped all reactions. Our patients are much more amenable to study of the monosynaptic reflexes, the internuncial pools, and so on.

Where are we then with the pyramidal tract? Man does not give us a good preparation. Natural lesions in the so-called pure culture of the pyramidal tract at the pyramids proper are too rare. Lesions of area 4 do not test the entire pyramidal tract. Only 3 per cent of the fibers come from Betz cells, probably those for fine digital movements. Cells of origin come from other cortices. Electrical stimulation experiments, while informative, are artificial and do not stimulate the normal bombardment of an area. Movements may be elicited from secondary motor points in the cortex other than area 4. Even stimulation of the occipital lobe gives eyeball movements.

"Natural lesions" – strokes in the internal capsule – involve extrapyramidal as well as pyramidal tract fibers. Dr. Lassek has shown that 57.5 per cent of paralyzed patients have no evidence of pyramidal tract involvement. Tumors ordinarily produce no pyramidal tract degeneration, although paralysis is present. In congenital lesions the pyramidal tract is frequently intact, although pronounced paralysis is present. Certain diseases, tumor, vascular disturbances, and trauma lead to facilitation or sensitization of cortical neurons to set off a movement pattern – a convulsion. In area 4 the pattern is typical, a jacksonian seizure, but the convulsion may be elicited from elsewhere and even an anencephalic monster with no cortex can have typical clonic seizures, as can animals transected just above the medulla.

It would appear that the pyramidal tract in man activates individual muscles selecting prime-movers, coordinating agonists and antagonists to produce skilled movement. It facilitates the segmental mechanism, but the nature of the terminations about internuncial neurons and anterior horn cells is still unclear. The extrapyramidal system sets the stage by coordinating the postural adjustments necessary for the easy and rapid performance.

How does the pyramidal system initiate motion? The most profound paralysis in man ensues, not when both areas 4 are removed, but when the parietal cortex is extirpated. Relearning or rehabilitation is quite rapid after area 4 destruction but impossible when the parietal cortex is out. Is the pyramidal tract, like so many other structures such as the spinal cord, dependent on the sensory system? The English school, from Sherrington through Walshe and Gooddy, look upon the pyramidal tract as an internuncial, a common pathway whereby the sensory system initiates and continuously directs the activities of the neuron motor mechanism. There is much to be said for this, and I note that Dr. Lassek, too, suggests that the pyramidal tract does not function as a self-sufficient unit but as part of a sensory-motor continuity.

Tonight, 2,400 years after the first demonstration that a lesion of one side of the head causes a paralysis of the opposite side of the body and about 246 years since Mestichelli and Petit, particularly, described the essential anatomic features of the pyramidal tract, we are still wondering about its function. However, we have learned much and have opened new vistas. We have the surviving isolated spinal cord segment in man, with an untapped physiology. The mechanism of the facilitation and suppression of movement in the human from point of initiation, through its circuits and termination at the segmental level, has been touched but not explained. The reason for reflexes appearing and disappearing with alterations in nutrition, infection, and body temperature remains a mystery. All these and

more, among them the pyramidal tract, belong to the realm of the still unsolved.

MODERATOR: The members of the panel have several questions.

DR. LASSEK: I have a question I'd like to ask Dr. Woolsey. In terms of spasticity and flaccidity, what do you think accounts for the diametrically opposite conclusions obtained by the several investigators who have ablated area 4 or sectioned the pyramids?

DR. WOOLSEY: First of all, as you know, not all agree on the definition of area 4. The main discrepancy in the results, according to our experimental findings with Travis, depends on the extent of the cortical lesion. Total removal of the precentral motor area, as we have defined that area, does not produce spasticity. Spasticity occurs only when the supplementary motor area is damaged in addition to the precentral motor area. The lesions in Fulton's animals which showed flaccid paralysis were confined to the caudal part of the precentral motor area. The spasticity producing strip lesions of Hines all involved the medial wall of the hemisphere in the region of the supplementary motor area. Dr. Hines emphasized that the lesion must involve the medial wall. I believe that involvement of the supplementary motor area also explains the spasticity produced in the experiments of Denny-Brown and Botterell. With respect to section of the pyramids, it is my opinion that the only precise experiments of this type were those of Tower, who failed to find spasticity in the cat, monkey, and chimpanzee. I suspect that, when spasticity has been reported following pyramid section, the lesions were not limited to the pyramid.

DR. WALKER: I'd like to ask Dr. Woolsey one question. What is the evidence that subcortical structures will take over motor function in the absence of all pyramidal tract connections?

DR. WOOLSEY: I suppose Dr. Walker may be referring to the fact that Dr. Travis and I have had some success in totally decorticating monkeys and, by adequate care, keeping them walking. From this we have concluded that subcortical centers in the monkey have potentially greater functional capacities in the absence of the cortex than has hitherto been granted them. It would be my opinion that these subcortical centers do not take over the functions of the pyramidal tract but that they contribute to motor function in the decorticated animal only those activities with which they have to do in the intact animal.

QUESTION: I suspect Dr. F. M. R. Walshe has answered this question for us, but it is directed to Dr. Woolsey. Since electrical stimulation at specific points of the cerebral cortex produces movements which vary widely, depending upon the pre-existing positions of the parts moved and other variable factors, how can we legitimately assume that electrical stimulation effects in any true sense the normal physiologic activity of the points stimulated? In other words, how can electrical stimulation reveal what happens in normal motor activity?

DR. WOOLSEY: I don't see how it can, anymore than any other artificially-induced activity of the nervous system reveals "normal" function. However, I do not see that this is an argument against carrying out experiments of this type. One is attempting to analyze the system under experimental conditions that one can more or less control. With the system stabilized under barbiturate anesthesia, I believe we are dealing primarily with the organization of the motor pathways as they leave the cortex. Under these conditions, reasonably reproducible results from animal to animal can be obtained. It is important to know the organization of the system at this level, for this organization must be basic to the normal functioning of the cortex, just as is the anatomic organization of other parts of the nervous system.

MODERATOR: A question directed to Dr. Lassek is as follows: Is there anatomic evidence for the origin of pyramidal fibers from sources other than the cerebral cortex?

DR. LASSEK: The latest work by Brodal and Walberg in the cat, to which we have already referred, makes it necessary to consider ascending fibers in the pyramidal tract. The nucleus gracilus and nucleus cuneatus are thought to be the origin of these. In respect to descending fibers with subcortical origin, I have been able to find only one report indicating that some of the fibers might be of subcortical origin and that was by Swank in 1936. This study was in the low ranking mammal, rabbit.

DR. WOOLSEY: May I comment on this question? Silver stains on specimens taken from wholly decorticated animals show very little in the way of fibers in the pyramid. However, this should be examined more carefully.

DR. LASSEK: I am pleased to have this information. The question might then be answered by stating that there is no evidence that the small gamma fibers of the pyramidal tract have origin in the reticular substance.

MODERATOR: A question to Dr. Lassek. Do the large fibers of the pyramidal tract have a special function? Is there an increase in the number of such fibers with age from infancy to childhood?

DR. LASSEK: Yes, there is an increase in the number of large fibers following birth but not an increase in the total number of fibers. I think that all of the pyramidal tract fibers are present at birth but it takes about two years for them to maturate. During this development, some fibers become larger and larger and appear to overshadow the others. In old age the large fibers tend to disappear and the pyramidal tract shrivels. However, not many cases have been studied carefully from that particular angle.

I don't know what the specific function of the large fibers is. I wish that I did. On the basis of electrophysiologic studies, there is some indication that they may be concerned with basic movements, particularly of the fingers, whereas intermediate-sized fibers may be distributed to the larger muscles such as the trunk and shoulders.

MODERATOR: This question is directed to Dr. Boshes. How does the level of a cord transection affect the extensor plantar reflex?

DR. BOSHES: It has been our observation that the higher the transection, the more complete the mechanism in the isolated segments of the cord. In a patient with a cervical transection many reflexes, flexion synergy, and Babinski signs are found.

MODERATOR: Another questioner wishes to know if the quality of the extensor plantar reflex is affected by quantitative section of the pyramidal tract in the spinal cord.

DR. WALKER: There are a number of factors which enter into this. In the first place, it is not likely that an injury of the cord is confined to the corticospinal tract only. The extensor plantar response is more likely to be present when the injury involves the corticospinal tract than if the lesion is in other portions, especially the anterior part. There must be a certain minimal threshold damage before the extensor plantar response is obtained, but I don't know that I can quantitate it. Possibly Dr. Boshes has some data on this.

DR. BOSHES: No, I definitely could not quantitate it. In analyzing our data and those published by Nathan and Smith from England, it was not only impossible to quantitate the lesion from the Babinski response, it also was not possible to anticipate it.

■ Above and below the decussation of the anterior pyramids of the medulla oblongata the conductors which have to do with sensation and voluntary motion are arranged differently in the spinal cord. Above this point, the sensorial and volitional conductors belonging to one side of the body lie together in the same lateral half of the cord, and this half is that which appears to belong, not to the same side of the body, but to the opposite side; at this point, the volitional conductors separate from the sensorial and pursue a different course to what is the common destination of both conductors alike, the volitional conductors crossing over at once and in a body to the other side of the cord and passing down this side until each one reaches the particular anterior root at which it emerges, the sensorial conductors passing down the same side of the cord and not crossing over to the other side (where they rejoin the volitional conductors) until they arrive at the level of the particular posterior roots with which they are connected. In other words, the sensorial and volitional conductors of the two sides of the body decussate, both of them, in the spinal cord, but not in the same place, the decussation of the volitional conductors being confined to the narrow path where the anterior pyramids of the medulla oblongata intercross, the decussation of the sensorial conductors being all along the spinal cord from one end to the other.—C. B. RADCLIFFE in *On Diseases of the Spine and of the Nerves,* published in 1871.

CASE REPORT

Cerebral Mucormycosis

A Fatal Fungus Infection Complicating other Diseases

J. C. Merriam, Jr., M.D. and C. G. Tedeschi, M.D.

THE TERM MUCORMYCOSIS is generally used to designate infection by either *Rhizopus* or *Mucor*, both belonging to the *Phycomycetes*. *Rhizopus* is characterized by root-like structures and by terminal sporangia arising from non-branched sporangiophores, which in turn sprout in fascicles at the point of rhizoid formation. *Mucor* also grows by numerous sporangiophores and shows terminal sporangia, but differs from *Rhizopus* inasmuch as it is not provided with rhizoids.

Early observations of mucormycosis in humans and animals fall naturally in two groups. One group includes cases characterized by the presence of the fungus as a secondary, accidental invader, and the other group includes cases in which the fungus is the primary cause of the disease.

Fürbringer[1] is credited with the first description of human mucormycosis in 1876. In his observations the fungus had played the role of secondary invader, incidental to gastric carcinoma in one case (male aged 66) and to severe gastroenteritis in another (male aged 31). A few walnut-sized hemorrhagic nodules were present in the lungs, and within these nodules hyphae 4 to 20 microns thick with club-shaped projections, sporangia, and columellae were recognized microscopically and interpreted as "*Mucor*." The cases of Cohnheim,[2] Podack,[3] Lang and Grubauer,[4] and Wätjen,[5] in which a fungus with the same characteristics was found in the lungs incidental to other disease, belong to the same group.

The first indication that two mucoraceae commonly occurring in bread (*M. rhizopus* and *M. corymlsifer)* can be pathogenic in dogs came from Lichtheim.[6] Shortly thereafter, Paltauf[7] reported the case of a 52 year old laborer who died after a short illness characterized by severe, crampy abdominal pains, epigastric tenderness, jaundice, ascites, and enlarged liver and spleen. Postmortem examination showed a laryngeal phlegmon, disseminated abscesses in the lungs and brain, and ulcerative lesions in the large intestine which had resulted in perforation and peritonitis. In all these various localizations hyphae 3 to 6 microns thick with warty excrescences and sporangia were shown, and he felt that the mucormycosis had originated in the intestines and spread to the other organs by permeation of fungi into the blood vessels, several of which were thrombosed and showed necrosis and inflammation of the walls.

Although this condition has been known in Europe for about 75 years, it was only in 1943 that a report by Gregory, Golden, and Haymaker[8] focused attention on the occurrence of mucormycosis in the United States. They reported three cases, all in adults, characterized by a triad of symptoms: uncontrolled diabetes (proved in two cases and probable in the third), unilateral panophthalmitis, and signs of disorders in the central nervous system rapidly followed by death. In all three cases a fungus thought to be *Mucor* was recognized at postmortem in various portions of the brain and meninges, in one or more of the cranial sinuses, and in the periorbital tissues of the involved eye. Internal carotid arteries and other cerebral blood vessels as well as dural sinuses were also the site of fungal invasion and there was associated extensive thrombosis. The pituitary gland was involved in two of their cases.

Six comparable cases of cerebral localization were reported thereafter[9–14] (table 1). Age, sex, and race give no clues as to the predisposing factors, and children do not escape this condition. Of the six cases so far reported, two were in infants[12,13] and one in a five year old girl.[14] In all these observations the fungal infection had developed on the ground of a preexisting debilitating condition, diabetes in three cases,[9–11] glomerulo-

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nephritis in two others,[12,14] and protracted diarrhea in one.[13] Evidence of associated unilateral panophthalmitis was found in only four cases.[9–13] It is, therefore, apparent that fungal invasion of the central nervous system can develop as a terminal event, not only in diabetes but also in other debilitating diseases, and that involvement of the eye does not occur constantly.

Whereas the nasal and paranasal sinuses are the most likely portal of entrance of the fungus in cerebral mucormycosis, aspiration of the same type of fungus in the respiratory tract gives rise to a comparable entity known as "pulmonary mucormycosis."

According to Baker,[15] this seems to be a new disease in the United States and one of increasing frequency. As in the cerebral form of mucormycosis, age, race, or sex are not important predisposing factors, but a debilitating condition of some type, such as antecedent diabetes, leukemia, severe burn, or infection, is found in the history of every reported case. Four cases of pulmonary mucormycosis from the recent literature,[15,16–18] to which six new case reports have been added, have been discussed by Baker.[15] Two of these cases[13,16] also had cerebral mucormycosis, and in case 6 of Baker's series the liver and spleen were affected by the fungus, as well as the lungs. In Zimmerman's case,[18] a 53 year old Negro with multiple myeloma treated with urethane, cortisone, and irradiation, both heart and lungs were affected by mucormycosis. Since spread of the fungus from one to another organ or system by arterial, venous, and lymphatic permeation occurs and the primary portal of entrance cannot be established with certainty in all instances, cases characterized by multiplicity of localizations are difficult to classify within the rigid scheme of pulmonary and cerebral mucormycosis and they are better fitted into a "multiple localizations" category.

Chest pain, pleural friction rub, production of bloody sputum, fever, and leukocytosis were present in some of the cases of pulmonary mucormycosis analyzed by Baker and, although the nature of the agent was not suspected, the existence of a pulmonary infection was established clinically. In some other cases the pulmonary lesions were incidentally disclosed at necropsy, and in a few other cases in which the patient recovered[19–21] the condition was recognized clinically by identification of the organism in sputum cultures. However, since the fungus is a common contaminant, its detection is not sufficient in itself to establish the

TABLE 1

Author	Year	Sex	Age	Preceding Illness	Acidosis	Orbital Infection	Vascular Thrombosis	Involvement of C.N.S.	Spinal Fluid	Estimated Duration of
Gregory et al.[9]	1943	F	43	Diabetes, 2 yr.	+	+	Cavernous sinus Circle of Willis	Meninges frontal lobes		3 days
		M	52	Diabetes, 5 yr.	+	+	Cerebral vessels	Inferior frontal lobes	295 cells, 80% polys	5 days+
		M	75	?Diabetes (histologically)		+		Meninges brainstem		2 days+
LeCompte and Meisner[9]	1947	M	57	Hemochromatosis	+	+	Cerebral vessels	Meninges brainstem		2 days
Wolf and Cowan[10]	1949	M	42	Diabetes, 15 yr.		+	Cavernous sinus	Meninges orbital surface of frontal lobe	150 cells, 80% lymphs	10 days+
Stratemeier[11]	1950	F	32	Diabetes	+	+	Cerebral vessels	Orbital surface of frontal lobes	"28 cells"	2 days+
Kurrein[12]	1954	M	5 mo.	Nephritis, 5 weeks	—	—		Meninges orbital surface of frontal lobe		5 weeks
Martin et al.[13]	1954	M	2½ mo.	Diarrhea, 2 weeks	—	+	Internal carotid artery	Meninges orbital surface, frontal lobe	0 cells, T.P. 208 mg.	8 days
Gunson and Bowden[14]	1955	F	5 yr.	Nephritis	—	—	Internal carotid and middle cerebral arteries	Temporal lobe		10 days
Our case		M	57	Diabetes	+	+	Internal carotid and cerebral arteries	Pons left cerebral peduncle	237 polys 51 lymps	8 days

diagnosis. Regardless of the organ involved the lesion of mucormycosis is mainly characterized by two categories of changes: 1) a mild non-specific type of inflammatory response, and 2) tissue necrosis and hemorrhage secondary to the ischemia that results from permeation of the fungus into the blood channels, with ensuing thrombosis. A coagulation type of necrosis was noted repeatedly, and in case 7 of Baker's series there were numerous giant cells, phagocytosis of hyphae, abundant lymphocytes, and increased eosinophils; in none, however, of the cases so far reported in human beings was the tissue reaction found to express itself by a granulomatous type of response, morphologically resembling tuberculosis, such as has been described in domestic animals.[22] Polymorphonuclear infiltration is the most common reaction to the fungus.

It has been indicated from various sources that drugs which inhibit bacterial infections favor the development of mycotic infection. This has been shown to be particularly true for the increased invasiveness of *Candida albicans*. As Baker[15] suggests, it is not unlikely that the apparent increase in mucormycosis may also be due to the broad use of antibiotics, which suppress bacterial growth and favor invasion of the fungus. Since no chemical agent is available which has a specific effect on the fungus, any new case added to the meager series of observations so far reported emphasizes the necessity of cautious treatment of the predisposing conditions.

CASE REPORT

A 57 year old white male cemetery superintendent was admitted to the Boston Veterans Hospital on August 22, 1955, because of left facial weakness of two days' duration. The present illness commenced one week before admission, when he noted the onset of left-sided steady headache, which gradually became more severe and was associated with several episodes of vomiting. Three days before admission the left eye became bloodshot and lacrimated excessively. His family physician gave him "red capsules" to take every eight hours "for the infection." Two days before admission the left eye became swollen and shut and the left side of the face felt "frozen." He stayed in bed, except for going to the bathroom, and was able to keep down a small quantity of liquids. On the day of admission he fell as he was going to the bathroom and it was decided to admit him to the hospital. The past history was uneventful except for a myocardial infarction 17 years previously and infrequent convulsive seizures, the first of which started three years previously and the last one occurred eight months before admission.

Physical examination revealed a well-nourished but dehydrated middle-aged male, somewhat drowsy, who was breathing deeply and sweating. Temperature was 99° F., pulse 110, respirations 28, and blood pressure 170/90. Left facial weakness was apparent. The left eye was proptosed, with chemosis of the conjunctiva and dilated fixed pupil. The cornea was cloudy, preventing visualiaztion of the fundus. Right eye and fundus were normal. Lungs were clear and the heart was slightly enlarged to the left. Abdomen was negative. On neurologic examination paralysis of the third, fourth, and sixth left cranial nerves was found, with absent pinprick sensation over the upper left face. Muscular movements of the right arm were weaker than the left.

Laboratory studies. Hemoglobin 14.9 gm., hematocrit 46, corrected sedimentation rate 16. White count 23,800, with 7 per cent bands, 80 per cent polymorphonuclear cells, 13 per cent lymphocytes. Urine contained no albumin, but showed a 4+ sugar and acetone reaction, and the sediment contained many granular casts and three or four white cells per high-powered field. Nonprotein nitrogen 47, blood sugar 346, carbon dioxide combining power 4.2 mEq. per liter; blood acetone strongly positive. Skull and chest films were negative.

Bacteriologic investigation yielded the following results: left conjunctiva, Gram-positive cocci in pairs, and Gram-positive rods in the smear; culture grew out *Staphylococcus albus* and diphtheroids. Urine, sterile. Sputum, Gram-positive cocci in pairs, and Gram-positive rods in the smear; culture grew out *Staphylococcus aureus*, coagulase negative, yeast-cells, and *Staphylococcus albus*. Spinal fluid, sterile.

Course. A diagnosis was made of diabetes, with acidosis, and cavernous sinus thrombosis. After cultures were taken he was started on intravenous fluids (half fructose, half normal saline), regular insulin 100 units stat, intramuscular aqueous penicillin, one million units every three hours, and intramuscular streptomycin, 1 gm. every six hours. Lumbar puncture was performed, with removal of clear fluid under normal pressure containing 288 white cells, of which 237 were polymorphonuclear cells and 51 lymphocytes. No microorganisms were recognized in the sediment. The acidosis gradually lessened and, after six hours and 500 units of insulin, his urine was negative for acetone, but the right side became flaccid and he went into deep coma. Terminally, his blood pressure fell to shock level and he developed cardiac arrhythmias not responding to Levophed and Pronestyl. He expired one day after admission, eight days from the onset of the present illness.

Postmortem findings. Autopsy three hours after death showed a well-developed and nourished middle-aged male. The left eye was closed, somewhat proptosed, and felt softer than the right; the skin around the eye had ecchymotic discoloration which extended over the bridge of the nose. The conjunctival surfaces were granular and reddened,

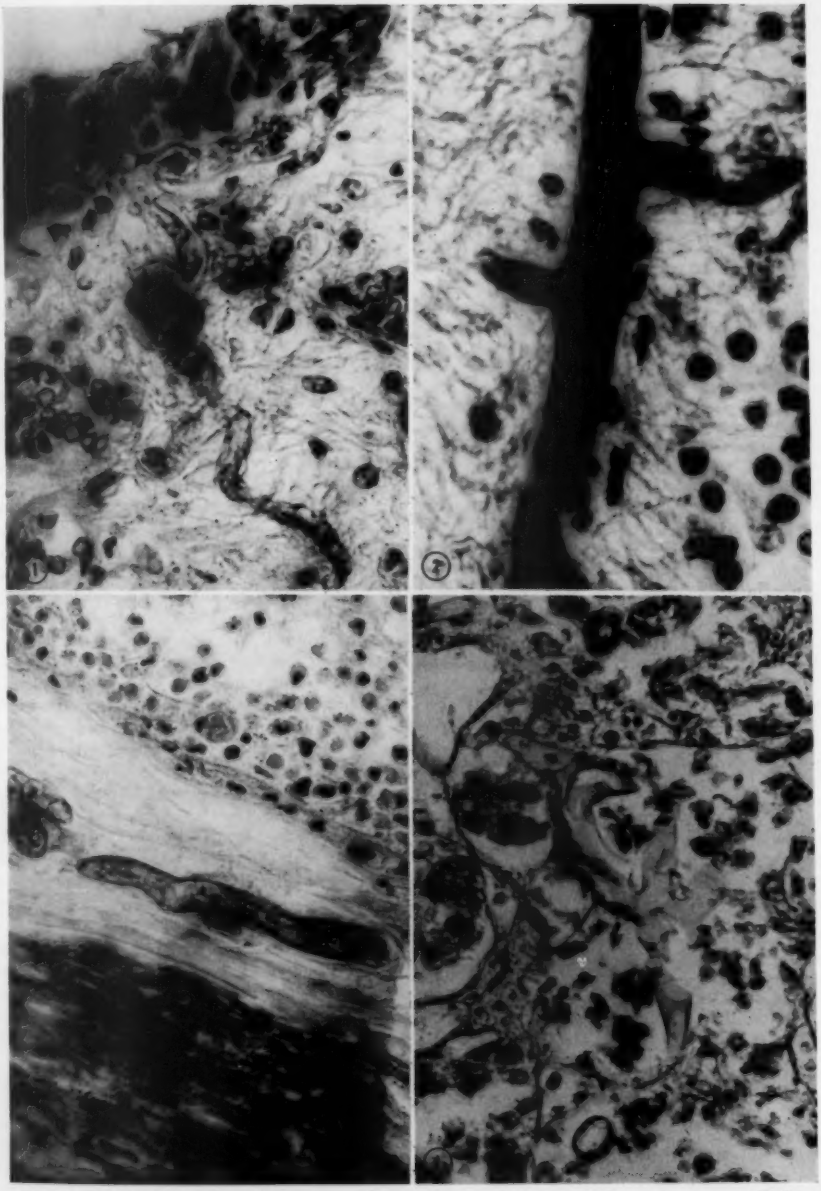

FIG. 1. Sphenoid sinus mucosa, showing coarse, non-septate hyphae of fungus interpreted as mucor. Notice the concurrent minimal inflammatory reaction. The epithelium lining the mucosa (at top of photomicrograph) is fairly well preserved. Hematoxylin-eosin stain.

FIG. 2. Branching hypha of mucor in the pons. A few round cells and polymorphonuclear cells are present in proximity of the fungus. Hematoxylin-eosin stain.

FIG. 3. Wall of carotid artery, showing coarse, branching, non-septate fungi embedded in the intima. Notice in the lumen above crowding of polymorphonuclear cells, "ghosts" of red cells, and cellular debris, interpreted as early formation of thrombus. Hematoxylin-eosin stain.

FIG. 4. Branching hyphae of mucor embedded in the anterior lobe of the pituitary gland, showing massive necrosis. Hematoxylin-eosin stain.

the cornea dull red, and the iris scarcely visible.

Examination of the organs within the thoracic cavity showed brown to black liquid material in the trachea and bronchial tree. Both lungs were congested and disseminated foci of early bronchopneumonia were shown microscopically. The heart weighed 420 gm. and had an area of thinning and scarring in the anterior wall of the left ventricle near the apex. The left anterior descending coronary artery was essentially occluded near its origin, and the right coronary artery was also occluded 3.5 cm. from its origin. These were occluded by dense atheromatous material and there was associated calcification of the vessels' walls.

Abdominal viscera were unremarkable except that the contents of the stomach, duodenum, and jejunum were black and tarry. No bleeding point could be discerned in mucosal surfaces, however.

The brain weighed 1500 gm., was edematous, and showed thickening and opacity of the leptomeninges covering the left side of the pons and left cerebral peduncle, which was somewhat softened. Left internal carotid artery, left middle cerebral, anterior cerebral, posterior cerebral, and superior cerebellar arteries were occluded by dark, reddish-brown thrombi. The left portion of the cavernous sinus, the sphenoid sinus, and the ethmoid sinuses had dark red-brown mucoid contents and they were lined by dark red mucosa, dull and disrupted in places. The tissues of the left orbit were reddened and edematous. Middle ears were normal.

Bacteriologic findings. Cultures taken at autopsy from the heart's blood yielded no growth; material obtained from the sphenoid sinus showed a few yeast-cells in the smear and grew out yeast-cells (not further identified) and a *Staphylococcus aureus,* coagulase negative, on culture.

Microscopic findings (abstract). On microscopic examination, masses of broad branching hyphae were seen in the mucosa lining the sphenoid sinus (figure 1), in the orbital contents, in the pons (figure 2), and in the meninges. In the hematoxylin-eosin-stained sections, the hyphae displayed a pale basophilic tinge and their outlines were better brought out by the periodic acid-Schiff method which revealed them as non-septate hollow tubes. In the sections stained according to the Ziehl-Nielsen method, they failed to reveal acid-fast properties and, in the Gram-stained sections, they could be classified as Gram-negative organisms. These results agree with the observations of Kurrein.[12] Similar hyphae in string-like arrangement were present along the walls of cerebral (figure 3) and meningeal blood vessels, both arteries and veins, several of which showed necrosis and recent thrombotic occlusion. In the areas involved by fungus permeation, there was from minimal to moderate inflammatory-cell infiltration, mostly polymorphonuclear cells and less numerous lymphocytes; associated degenerative changes in neurons were shown in the left frontal cortex and pons. The pituitary gland was also involved and a large portion of the anterior lobe was infarcted (figure 4). Particularly in these necrotic areas there was heavy polymorphonuclear infiltration which extended into the fibrous capsule of the organ. No fungi were found in any of the other organs examined.

Since the patient presumably had had diabetes, particular attention was brought to the condition of the pancreas and kidneys. The pancreas was seen to be essentially normal, with islets not unusual in number, distribution, or structure. No evidence was found of intercapillary glomerulosclerosis and, except for minimal atherosclerotic changes, the kidneys also were not remarkable.

DISCUSSION

Definitive diagnosis of mucormycosis cannot be made without cultural confirmation. In our case, the yeast-cells growing in the cultures of the sphenoid sinus were thought to be contaminants. The culture of the sputum also grew out yeast-cells, which may be assumed to be contaminants, since fungi were not noted in the lungs at autopsy. None of the cases summarized in this paper had cultural confirmation of the diagnosis of mucormycosis, but the fungus is identifiable morphologically by its broad, branching, non-septate hyphae.*

The clinical syndrome of diabetes out of control, a red bulging eye, and the rapid onset of neurologic symptoms leading to death are sufficiently dramatic to focus attention on this fungus infection. Seven of the ten cases analyzed in this paper were characterized by this triad of symptoms. Zimmerman, however, pointed out in a recent article[18] that a number of cases, soon to be published, are being studied at the Armed Forces Institute of Pathology and that very few of these had evidence of diabetes or ophthalmitis, though these have occurred in other debilitating and terminal diseases.

In the cases reported since 1949, nearly every antibiotic and combination of antibiotics, together with anticoagulants in one case, have been tried therapeutically. Our patient was submitted to intensive penicillin and streptomycin treatments, but signs and symptoms of disorders in the central nervous system were already present at this time and it is presumed that fungal infection was already set in when the treatment was initiated. The total duration of the illness in our case was eight days; in other comparable cases it has ranged from two

*Microscopic sections of our cases were studied by Dr. P. M. LeCompte, who found the organism to be compatible in all respects to the one described in his case report. Dr. Herbert Mescon, consultant to the Veterans Hospital in dermatology and fungus diseases, also reviewed some of the material and stated that the organism was compatible with mucormyces.

to ten days. It is strange that an organism of such low virulence as mucor should cause such a fulminating and lethal disease. The role played by associated organisms should, however, not be overlooked. Mixed infections have been described in concurrence with mucor. In our case Gram-positive cocci in pairs and Gram-positive rods were shown by smears taken during life from the left conjunctiva of the involved eye, and a *Staphylococcus albus* grew on culture from the same material. A *Staphylococcus aureus*, coagulase negative, was obtained from the sphenoid sinus at autopsy. These mixed infections probably indicate diminished resistance of the body to infections in general, and ensuing pathology should therefore be interpreted on the basis of bacterial and fungal synergism. Fever and leukocytosis are other frequent accompanying features both of cerebral and pulmonary mucormycosis. Despite an almost normal temperature, the peripheral blood count in our case also showed marked leukocytosis, an expected reaction to the overwhelming infection. On the other hand, the inflammatory response in the tissues was relatively mild, and it is felt that thrombosis accompanying the intravascular growth of the fungus must account for most of the damage.

SUMMARY

A case is reported of cerebral mucormycosis in a 57 year old white male, admitted to the hospital with diabetes, panophthalmitis, and rapidly developing neurologic symptoms which progressed to hemiplegia, coma, and death. The total course of the disease was eight days. Pathologic studies revealed extensive thrombosis of cerebral and meningeal blood vessels, both arteries and veins, secondary to the permeation of vessel walls by fungi identified morphologically as mucor. Focal ischemic necrosis with minimal inflammatory response was found in the brain, particularly severe in the pons and pituitary gland. The sphenoid sinus and orbit were also involved, and it is felt that the portal of entry could have been from either of these two sites.

Nine comparable cases of cerebral mucormycosis from the literature are reviewed. Common pertinent features are preexisting debilitating diseases (often, but not necessarily, diabetes), panophthalmitis, and rapidly developing neurologic symptoms, proceeding to death.

It has been indicated from various sources that drugs which inhibit bacterial infections favor the development of mycotic infections. The incidence of pulmonary mucormycosis is apparently increased; greater incidence of mucormycosis in other localizations, including the central nervous system, can be expected to occur due to the broad use of antibiotics which suppress bacterial growth and favor invasion of the fungus.

Financial assistance for procurement of reprints was provided by the Gray Pharmaceutical Company, Newton, Massachusetts.

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CASE REPORT

Hydrocephalus as a Sequel to Lymphocytic Choriomeningitis

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NEUROLOGIC SEQUELAE following lymphocytic choriomeningitis are uncommon. The occurrence of arachnoiditis secondary to this type of meningitis is rare.[1,2] Barker and Ford's patient was a 37 year old woman who developed spinal arachnoiditis, proved by laminectomy, a few months after the acute meningitis had subsided. Baker's case was a man who died after an illness of nine years. Autopsy revealed severe arachnoiditis covering the entire brain, along with alterations in the cerebral substance. Others[3,4] have also described the pathologic findings in fatal cases of lymphocytic choriomeningitis, but the only changes in the meninges consisted of cellular infiltration. The present report concerns another instance of arachnoiditis following lymphocytic choriomeningitis and leading to the development of a non-communicating hydrocephalus.

CASE SUMMARY

A 15 year old white girl was hospitalized on December 19, 1955. Five days ealier she had a painful lower molar tooth extracted which apparently was not infected. She remained in bed for the next two days because of malaise and a sore throat. Two days before admission she developed a frontal headache, low grade fever, moderate stiffness of the neck, and nausea and vomiting. These complaints had become progressively worse.

The past and family history were unremarkable. There was no known contact with mice or rats prior to this acute illness.

Examination revealed an acutely ill girl. She was oriented, moderately alert, and cooperative. The pulse was 104, respirations 20, blood pressure 120/80, and rectal temperature 103° F. The general physical examination was unremarkable. The neurologic examination was negative, except for marked nuchal rigidity. There was no papilledema.

The admission white blood count was 2,925 per cu. mm., with 43 per cent polymorphonuclear cells, 44 per cent lymphocytes, 4 per cent metamyelocytes, and 9 per cent monocytes. Hemoglobin was 14.5 gm. per cent. The blood serologic test for syphilis was negative. Urinalysis was within normal limits, except for two-plus acetone which subsequently cleared. A lumbar puncture done on the day of admission revealed 460 cells, 99 per cent lymphocytes, and 1 per cent polymorphonuclear cells; protein content of 190 mg. per cent; sugar 45 mg. per cent, with a simultaneous blood sugar of 110 mg. per cent; and an opening pressure of 170 mm. (table 1). Acid-fast, fungus, and routine cultures of the spinal fluid showed no growth. Two blood cultures on December 20 were sterile. A chest film was negative. Typhoid, paratyphoid, heterophil, proteus, and leptospira agglutinins were not demonstrable in significant amounts. Mumps, lymphocytic choriomeningitis (LCM), eastern and western equine and St. Louis encephalitis complement-fixing antibodies were present in less than 1:4 titer on December 20.

She was started on 600,000 units of procaine penicillin given daily for a total of seven days. On the fourth day her temperature returned to normal, the nuchal rigidity cleared, and she became asymptomatic, except for a mild frontal headache and infrequent nausea and vomiting. Blood serum drawn on December 30 showed a lymphocytic choriomeningitis complement-fixing antibody titer of 1:4. Four lumbar punctures were done during her hospital stay (table 1). She was discharged on January 3, 1956, still complaining of mild frontal headache.

She was seen in the out-patient department on five occasions, from January 7 to January 19, 1956. During each visit she complained of headache, at first frontal but later occipital. On January 9 a third sample of blood was drawn for determination of lymphocytic choriomeningitis complement-fixing antibody and the titer was reported to be 1:16. At this time she complained of weakness and clumsiness of the right arm. Examination disclosed weakness of this arm but no deep reflex asymmetry.

The patient was admitted to Duke Hospital

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FIGS. 1 and 2. Ventriculograms showing dilatation of all ventricles.

on April 4, 1956, with the chief complaint of occipital and frontal headaches and occasional vertigo. The occipital headache mentioned previously was at first intermittent, but later became constant and grew progressively worse. This became associated with a dull, constant, bifrontal headache. During the interval between hospitalizations, she had frequent episodes of vertigo, not associated with loss of consciousness, nausea, vomiting, or tinnitus. The weakness and clumsiness of the right arm mentioned on January 9 lasted one month. A few weeks before admission her visual acuity became slightly impaired, particularly in the left eye. She denied having had diplopia or lethargy.

Examination on April 4 revealed the patient to be oriented, alert, and in no acute distress. Her temperature was normal. The blood pressure was 110/64 and the pulse 72. There was no nuchal rigidity. The left fundus showed two diopters of papilledema, with three small flame-shaped hemorrhages near the disk border. The veins were moderately engorged and did not pulsate. The nasal margin of the right disk was slightly blurred, but within normal limits. The remainder of the examination was unremarkable.

The routine blood and urine examinations were within normal limits. Skull films taken on the day of admission were unremarkable. An electroencephalogram done on April 9 revealed the presence of large slow waves over all regions, but consistently more marked over the left hemisphere. A lumbar puncture was not done because of the presence of papilledema.

The patient was seen in consultation by the neurosurgical service and it was suggested that ventriculograms be done. However, the family was reluctant and signed the patient out of the hospital against advice on April 14.

During this admission, she continued to complain of headaches and mild vertigo. Her mental status and general condition remained unchanged. The papilledema in the left eye and blurring of the right disk margin showed slight progression.

The patient was re-admitted to Duke Hospital five days later, on April 19, 1956, because of an increase in the severity of her headaches. She had continued to have vertigo, but had not experienced nausea, vomiting, diplopia, or lethargy. She was alert and well oriented. The papilledema had progressed to three diopters in the left eye and to one diopter in the right. The pulse rate was 88 and the blood pressure 130/100. There was no deep reflex asymmetry noted at this time.

On April 23 bilateral posterior burr holes were made under local anesthesia and subsequent ventriculograms revealed dilatation of all ventricles, including the fourth ventricle (figures 1 and 2). On April 26 neutral phenolsulphonphthalein was injected into the right lateral ventricle, but none was recovered from the lumbar subarachnoid space after a lapse of 30 minutes. A pneumoencephalogram showed no filling of the ventricles nor were the basal cisterns visualized.

From these studies, the diagnosis of a noncommunicating hydrocephalus was made, presumably as a result of adhesions in and around the foramina of Magendie and Luschka. It was elected to relieve the obstruction by a ventriculomastoidostomy.[5] This was done through a small right posterior temporal craniectomy on April 27, 1956. The patient tolerated the operation well and her course was uneventful

TABLE 1
SUMMARY OF CSF EXAMINATIONS FROM DECEMBER 19, 1955 TO MAY 31, 1956

Date	*12-19-55*	*12-21-55*	*12-30-55*	*1-3-56*	*1-16-56*	*5-15-56*	*5-31-56*
Opening pressure mm. CSF	170	168	70	40	160	240	330
Appearance	clear colorless	colorless sl. cloudy	colorless sl. cloudy	clear colorless	clear colorless	clear colorless	clear colorless
White blood cells	460	257	505	190	44	6	10
% polymorphonuclears	1	1	1	0	4	0	0
% lymphocytes	99	99	99	100	96	100	100
Protein, mg. %	190	170	264	223	109	54	68
CSF sugar, mg. %	45	45	40	39	—	—	—
Blood sugar, mg. %	110	92	106	101	—	—	—

until the eighth postoperative day, at which time she developed a temperature of 103° F. and mild signs of meningeal irritation. On intravenous penicillin, improvement was noted within 24 hours and four days later she was asymptomatic.

The patient did not complain of headache at any time during her postoperative course. Lumbar puncture done on May 15 revealed an opening pressure of 240 mm., protein content of 54 mg. per cent, and six lymphocytes per cu. mm (table 1). The lymphocytic choriomeningitis complement-fixing antibody titer at this time was 1:4. There was a gradual subsidence of the papilledema during the postoperative period. She was discharged on May 16, 1956.

She did well until May 23, at which time she again experienced onset of headaches. These grew progressively worse and were associated with infrequent vomiting. She was re-admitted to Duke Hospital for the third time on May 30. Examination disclosed bilateral papilledema, worse in the left eye, but less marked in either eye than just prior to her operation. She was oriented and alert. The remainder of the examination was unremarkable.

A lumbar puncture was done on May 31. The opening pressure was 330 mm. and the protein content was 68 mg. per cent. There were 10 lymphocytes per cu. mm. (table 1).

Her course during this admission was uneventful. After the first day she ceased having headaches and at no time did she vomit. It was assumed that her symptoms were due to a transient block in the ventriculomastoidostomy. She was discharged on June 2, 1956.

When last seen in the clinic on November 29, 1956 she was free of symptoms and the papilledema had completely subsided.

COMMENT

The clinical form of aseptic meningitis was felt to be due to the virus of lymphocytic choriomeningitis from evidence derived from immunologic findings. The increase in the lymphocytic choriomeningitis complement-fixing antibody titer from less than 1:4 at the onset of her acute illness to 1:16 three weeks later is considered diagnostic, especially since all three specimens were determined at the same time against the same antigen. The drop in the titer to a level of 1:4 five months after her acute illness is in keeping with the findings of Smadel and Wall[6] who noted that lymphocytic choriomeningitis complement-fixing antibody disappears from the serum a few months after the illness.

The subsequent development of a noncommunicating hydrocephalus was presumably due to a posterior fossa arachnoiditis secondary to the meningitis.

In review of 21 cases of lymphocytic choriomeningitis, Green and others[9] state that two of their cases developed severe and prolonged headaches after meningitis. On re-admission for study of their complaint, these two cases showed increased intracranial pressure which required periodic spinal punctures for relief. Whether these two cases had hydrocephalus is not known since air studies were not done.

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CASE REPORT

Spinal Epidural Abscess Due to Friedlander's Bacillus

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NONTUBERCULOUS SPINAL EPIDURAL ABSCESS is usually due to infection by staphylococcus; this organism has been responsible in from 82 per cent to 100 per cent of cases in various reported series.[1,2] Less frequently, other gram-positive cocci are the causative agents. However, relatively few cases have been reported due to gram-negative organisms; in isolated instances *Brucella suis*,[3] *Pseudomonas æruginosa*,[4] *Salmonella paratyphii*,[5] and *Salmonella typhosa*[6] have been implicated, as well as several unidentified gram-negative rods and cocci (probably including *Neisseria gonorrhœæ*).

We have recently had the opportunity of managing a case of spinal epidural abscess in the lumbosacral region due to *Klebsiella pneumoniæ* (Friedlander's bacillus).

CLINICAL HISTORY

A 37 year old white male insurance agent was admitted to the Neurological Institute of New York on October 12, 1954 because of fever and back pain of six weeks' duration. Past history was significant in that 14 years prior to admission the patient had a partial lobectomy of the left lower lung for bronchiectasis. However, he had been free of respiratory symptoms since this procedure.

Nine weeks prior to admission he developed slight stiffness of the neck and myalgia, diagnosed as "grippe." Six weeks before admission he developed pain in the low back and buttocks, radiating down the posterior aspect of the thighs, and associated with a low grade fever. At this time he was treated with sulfonamides and intramuscular penicillin for several days, but these medications were discontinued when a generalized erythematous skin eruption occurred.

About four weeks prior to admission, his pain became more severe, fever rose to higher levels, and he was admitted to another hospital. There he was treated for "arthritis" with butazolidine and cortisone. Two weeks prior to admission he developed numbness over both hips and posterior thighs, the numbness subsequently spreading across his lower abdomen. Two days before admission urinary retention and constipation supervened and he was transferred to the Neurological Institute.

Physical examination revealed a well developed white male who appeared to be acutely and chronically ill. He was in marked distress from back pain and required narcotics for relief. Rectal temperature was 100.2° F. There was sacral tenderness and the lower lumbar muscles were tense. Straight leg raising was limited at 15° bilaterally. A thoracic scar was present and the breath sounds were altered in the area of the obsolete thoracotomy, but there was no evidence of active pulmonary disease. Blood pressure was 130/74, pulse 110. Examination of the heart was within normal limits. The abdomen was distended by a full bladder. Rectal examination revealed a moderately tight sphincter and a marked accumulation of feces.

The patient was right-handed. Gait was not tested. Nonequilibratory coordination tests were normal. There was moderate weakness of the flexors of the knees, the dorsiflexors and plantar flexors of the ankles and toes, the everters and inverters of the feet, and the abductors and rotators of the hips bilaterally, indicating that muscles in the distribution of L5, S1, and S2 were involved bilaterally. Deep tendon reflexes were active, except for the ankle jerks which were absent bilaterally. There were no pathologic reflexes. Sensory examination revealed a marked hypesthesia and hypalgesia over the distribution of S2 to S5 bilaterally, with a fading loss over S1 and L5 dermatomes. Cranial nerve examination was within normal limits.

The hemoglobin was 13.5 gm. per cent and the red cell count was 4.4 million. The white blood count was 8,000, with 72 per cent polymorphonuclear cells, 27 per cent lymphocytes, and 1 per cent monocytes. The nonprotein nitrogen in the blood was 31 mg. per cent, and the fasting blood sugar was 91 mg. per cent. Erythrocyte sedimentation rate (Westergren) was 51 mm. per hour. Urinalysis revealed a specific gravity of 1.020, one plus acetone, no sugar, no albumin, and a negative sediment examination.

Roentgenograms of the chest and spine were normal. Flat films of the abdomen showed moderate distention of the large intestine. Plain roentgenograms of the lumbosacral spine were

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interpreted as normal, but slight demineralization of the left pedicle of L5 was noted on the myelographic films. A myelogram was done with the needle at the L2-L3 interspace, and this revealed free flow of Pantopaque from L4 to the foramen magnum; however, at the inferior border of L4 the column of oil narrowed until it became point-like, no contrast medium passing caudad to this interspace. This appearance was interpreted as suggesting the presence of an epidural mass.

Spinal fluid obtained before the introduction of dye was clear and colorless, but contained 22 polymorphonuclear cells and 4 mononuclear cells per cu. mm. The cerebrospinal fluid protein was 192 mg. per cent and the sugar was 64 mg. per cent. Culture of the cerebrospinal fluid was negative.

Preoperatively opinion was divided as to whether the lesion was an epidural abscess or an epidural neoplasm, such as lymphoma. A laminectomy of L4 and L5 bilaterally was carried out on the second hospital day. Necrotic material was encountered in the epidural space, and macroscopically pus was not visible; the operator's impression was that this was probably a necrotic epidural tumor. Adequate decompression was accomplished by a partial removal of the mass, but the wound was closed because the patient developed a severe hypotension. The operative site was not drained. Microscopic examination of the removed material revealed the correct diagnosis to be epidural abscess. "The specimen consists of dense fibrous tissue in which there is an inflammatory reaction. On the surface of this membrane and in its superficial portion, there are polymorphonuclear leukocytes. In the tissue, in addition, there are lymphocytes, large mononuclear cells, and occasional plasma cells. Fibroblasts and capillaries are found emerging from the surface of the connective tissue membrane." Routine culture of the material grew out *Klebsiella pneumoniae*. In vitro the organisms were found to be sensitive to Aureomycin, Terramycin, and streptomycin. No anaerobes were present.

Postoperatively the patient recovered quickly from hypotension. He was treated with sulfadiazine, 2.0 gm. per day, and streptomycin, 1.0 gm. per day. He became afebrile and his intense pain gradually subsided. His inability to void continued and he was on catheter drainage for two weeks before spontaneous bladder function returned. Coincidentally the muscle weakness disappeared, the ankle jerks returned, and the area of sensory deficit diminished. Despite this improvement, however, a lumbar puncture performed three weeks postoperatively yielded fluid containing 13 lymphocytes, protein 279 mg. per cent, sugar 60 mg. per cent, and a negative culture. This was believed to represent continuing epidural inflammation. Tetracycline, 2.0 gm. per day, was now given in addition to sulfadiazine and streptomycin. In the next ten days the spinal fluid protein fell to 196 mg. per cent and the fluid became acellular. The patient was discharged to his home on November 18 to continue on sulfadiazine and tetracycline as an outpatient. By the end of December the spinal fluid protein had fallen to 78 mg. per cent and antibiotics were discontinued. One year after operation the patient was at work and asymptomatic, with a persistent minimal sensory deficit over S3-S5 dermatomes as the only residual.

DISCUSSION

Symptomatology. Epidural abscess of the spinal canal is said to be a condition in which the same "symptoms appear with monotonous regularity."[7] The case presented falls within the classic symptoms, despite the unusual etiologic organism. There is a history of an antecedent infection, followed after a brief interval by back pain and fever. The back pain was very intense, a characteristic feature of this illness.

The next stage in the usual course of pyogenic epidural abscess is the development of radicular symptoms, followed by signs of compression of intraspinal components. Ordinarily this occurs within a few days to one or two weeks after the development of back pain. In this case the sequence was somewhat delayed, radicular symptoms coming on after four weeks and cauda equina compression six weeks after the onset of pain. This may have been due to the nature of the infecting organism, but may also have resulted from the use of sulfonamides early in the infection. Also it is well to remember that approximately one-quarter of spinal epidural abscesses evolve symptomatically over a period of weeks or months; thus 15 of 88 cases (17 per cent) compiled by Browder and Meyers in 1937,[1] and 19 of 69 cases (27 per cent) reviewed by Grant in 1945[7] were classified as chronic in type. In these instances, fever and leukocytosis may be absent or minimal; preoperatively and by gross appearance at operation, these chronic lesions may be difficult to distinguish from other epidural pathology, such as sarcomas and lymphomas. Such pyogenic granulomas may show no definite signs of infection macroscopically, being dense fibrous masses, grayish-red in color, and usually adherent to the dura.[7,8]

Site. In this case the lesion was localized to the cauda equina. In the cervical area where the epidural space is only a potential one, spinal epidural abscesses are rare and it might be supposed that the lumbo-

sacral region where the epidural space is largest would be the most frequent site. Yet the published cases clearly indicate a preponderance of lesions in the upper thoracic region.[2,7,8] The reason for this is not clear.

Pathogenesis. Browder contended that spinal epidural abscess is always secondary to vertebral osteomyelitis. This contention is disputed,[9] others believing that bacteria brought by the blood stream may lodge directly in the epidural space. Certainly there have been many cases of epidural abscess that have been clearly secondary complications of a frank osteomyelitis, and this includes several of the cases due to gram-negative organisms.[5] More often, however, the osteomyelitis is subtle. In this regard it should be noted that roentgenograms have revealed evidence of osteomyelitis in as few as 18 per cent of cases in some series.[10] In the present case the only evidence of bony involvement was slight demineralization of the L5 pedicle seen on the roentgenogram, but at operation no gross infection of bone was seen.

Diagnosis. In the early stages of the disease, diagnosis may be exceedingly difficult. It is said that the combination of very severe localized back pain and fever, usually associated with localized spinal tenderness and limitation of straight leg raising, should be enough to suggest the diagnosis, which then can be confirmed by myelography and surgery. In practice the situation is more difficult and fewer than 5 per cent of reported cases of epidural abscess were diagnosed prior to the development of neurologic signs.[11,12] By the time the patient develops symptoms due to compression of spinal roots, cord, or cauda equina, the lesion is easily localized and its etiology readily suspected from the preceding history of infection, severe back pain, and general signs of infection. Clinical localization should, however, be confirmed by myelography when possible as the abscess is often more extensive than symptoms suggest.[8]

Treatment. The treatment of choice continues to be surgical drainage of the lesion. In this case the back was closed after incomplete removal of the lesion, due to the fact that the patient developed severe hypotension during the operative procedure. The wound was closed without drainage because of the operator's impression that he was dealing with an epidural neoplasm. By chance, the patient was allergic to penicillin and, therefore, was treated postoperatively with sulfadiazine and streptomycin rather than penicillin and streptomycin before the culture report was returned. This was indeed fortunate as the pathogenic agent proved to be gram-negative. However, inflammation persisted as shown by a spinal fluid protein of 292 mg. per cent recorded three weeks postoperatively. It was controlled, however, without further surgery by the reinforcement of antibiotic therapy with tetracycline.

SUMMARY

A case of subacute epidural abscess of the cauda equina due to *Klebsiella pneumoniæ is reported.* Most aspects of the case were similar to those previously reported, although the pathogenic organism was unique.

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Neurology

BOOK REVIEWS

Die Eigenart der kindlichen Hirntätigkeit

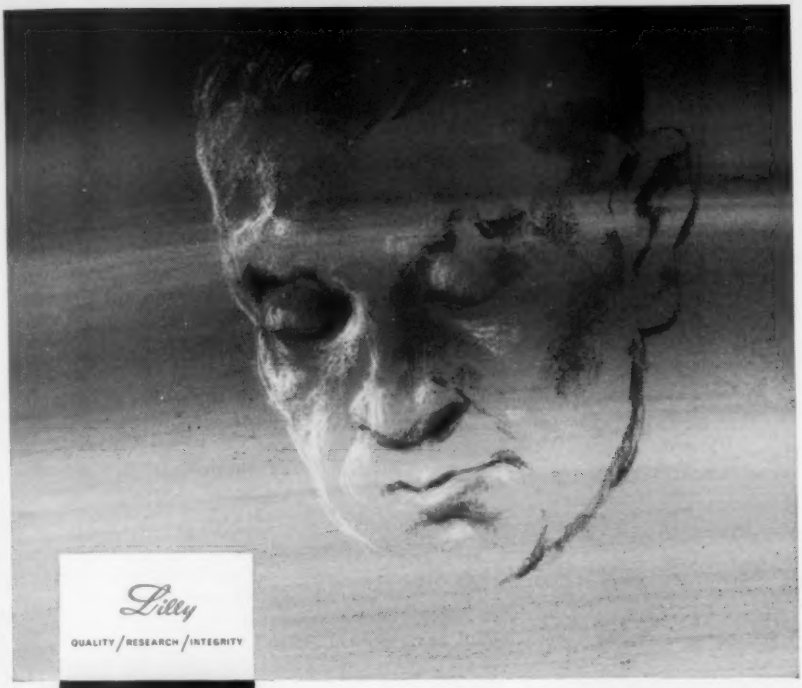
Albrecht Peiper. Leipzig: Georg Thieme. 2nd edition, 1956. 588 pages. D.M. 44.50 (bound).

MANY A NEUROLOGIST must feel a trifle embarrassed when asked to express an opinion regarding a small baby. The immature brain of an infant could hardly be expected to function in either health or disease like that of an older person. The working of an infantile brain is not fathomed, as Peiper aptly remarks, by memories of childhood recalled on the analyst's couch. Such knowledge can be gained only by careful observation from birth on of the child's motor activity and his responses to stimuli. Peiper and his associates in the Pediatric Clinic at Leipzig have been making observations of this sort for years. They have correlated their data with the teaching of experimental physiology, observations of animal behavior, phylogenetic history, and embryologic development. The second edition of Peiper's work is a veritable mine of information, representing German scholarship and scientific thoroughness at their best. The material is exceptionally well organized, with a concise summary and extensive bibliography at the end of each chapter. The illustrations are excellent. In addition to supplying needed information for pediatricians and neurologists, the work is a significant contribution to general biology.

The views of great philosophers and other outstanding thinkers are reviewed in the introductory chapter. Since sensory experience is the basis of intellectual development, the infant's responses to all manner of stimuli are described in the second chapter. A discussion of facial expression *(Mienenspiel)*, which likewise has a sensory basis, logically follows. Labyrinthine, postural, and righting reflexes are described in the fourth chapter. Tonic neck reflexes are occasionally observed in an incomplete form during the first six months but are more common in premature infants. Movements of progression are next taken up. Stepping and walking movements similar to those elicited in spinal preparations can be demonstrated during the early months and are then suppressed. The first step toward progression occurs when the baby rolls on its belly and raises its head. Spontaneous movements and the clinically important reflexes are considered in the sixth and seventh chapters. In an 80-page chapter on the neurology of respiration, various respiratory disturbances are discussed; eight pages are devoted to whooping cough. The neurology of nutrition is given even more space and is followed by a chapter on sleep. Infants are ideal subjects for the study of conditioned reflexes, which are considered in the eleventh chapter. Neural functions at different stages of development are then summarized. The newborn is referred to as *Pallidumwesen*, that is, a creature whose highest level of integration is in the globus pallidus. In his discussion of the influence of environment on the developing child, the author, as in previous chapters, is mindful of practical considerations. The concluding chapter is a summary of the entire work.

An English translation of this unique work is highly desirable, since many physicians do not have a sufficient knowledge of German to derive full benefit from reading the original.

L. E. D.



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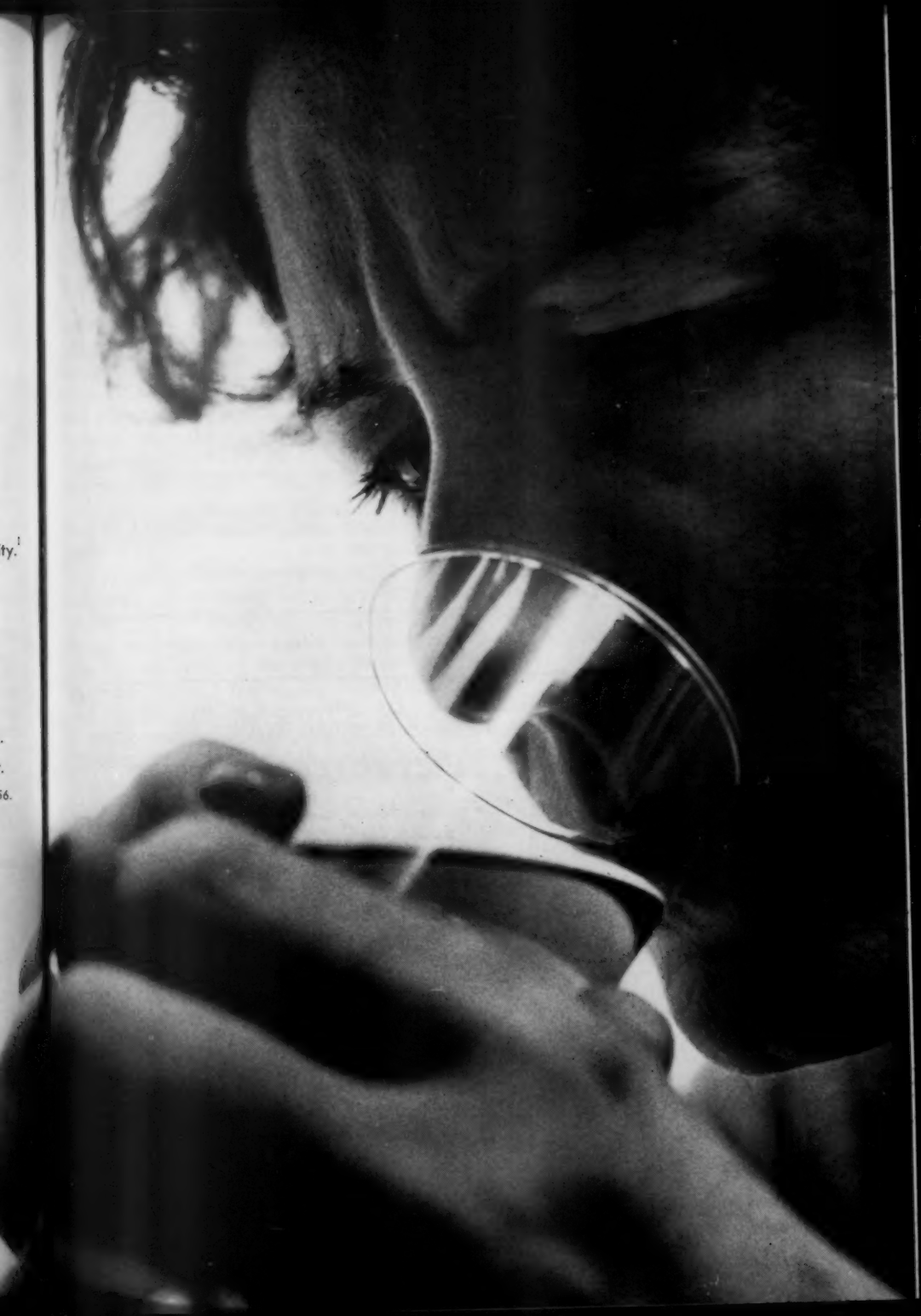

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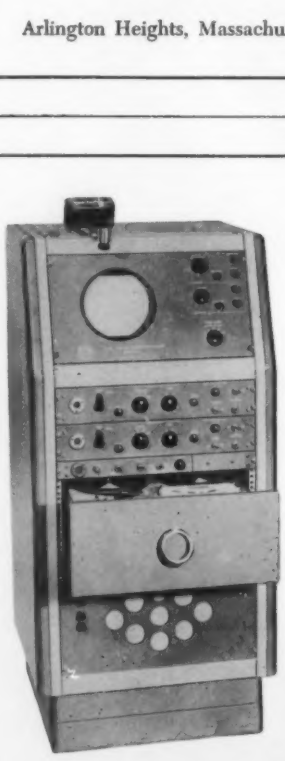

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NEWSLETTER

AMERICAN ACADEMY OF NEUROLOGY

International Congress Number

JULY 1957

A Tribute to the Brussels Congress

In the twilight of its tenth anniversary, the American Academy of Neurology (AAN) pays homage to the planning and dedication of the executive committee of the First International Congress of Neurological Sciences (July 21-28) in Brussels, Pres. P. van Gehuchten, Sec. Gen. Ludo van Bogaert, and their international colleagues.... Moreover, in anticipation of the coming anniversary, this number reviews highlights behind the story of the AAN, which within a decade has burgeoned into the largest neurologic society in the United States and the only one requiring its fellows to be qualified and predominantly interested in medical neurology. How did the AAN story begin?

Year of AAN Conception 1947

One night in Minneapolis in the fall of 1947, a young neurologist, Joe Resch, asked a question. How could he become actively affiliated with a national neurologic society? The same question was burning the lips of many other young neurologists of the day, who yearned to mingle with their contemporaries and seniors in a national gathering, but lacked the opportunity. However, Resch had occasion to fire his query at a reverberating target, A. B. Baker, dynamic professor of neurology at the University of Minnesota. Dr. Baker characteristically searched for a quick answer by writing 52 distinguished neurologists a letter (October 1947) in which he proposed the organization of a true neurologic academy in the United States. The replies were prompt to concur, which stirred Baker to translate his proposal into concrete action.

Year of Birth 1948

The AAN constitution and bylaws were incorporated in Minnesota (March 13, 1948) by A. B. Baker, with the able assistance of his former associate, Joe R. Brown (now at the Mayo Clinic). The recipients of the Baker proposal became AAN charter members.... Several months later on the hot, sultry evening of July 23, 1948, 50 of the 52 charter members convened in Chicago's Stevens Hotel to plot the future course of the nascent society. A. B. Baker was elected first AAN president and Joe R. Brown, the first secretary-treasurer. The first committees were appointed and a preliminary program was formulated.

Year of Socialization 1949

In May 1949 AAN membership had increased from the original 52 in 1947 to 442, the new members coming from almost everywhere in the United States. This rapid growth invoked a need for the new members to meet their seniors and for each to know and cultivate one another and to identify their interests with the AAN central mission for the advancement of neurol-

ogy. Thus, to engender a fraternal spirit directed toward a common goal became the initial AAN objective. The first AAN NEWSLETTER, designed to bond common interests through the dissemination of news, personal, scientific, and historical, appeared in May 1949. The rising spirit of camaraderie dominated the first annual AAN meeting held at the Spa resort of French Lick, Indiana (June 1-3, 1949). While the scientific sessions were well attended, almost equal attention was given to golf tournaments and other social events conducive to group fellowship. It was at this meeting also that the Woman's Auxiliary was formed and began to develop its important role of maintaining a climate of group identity in the Academy.... Later in the fall of 1949 this lively spirit of fraternization and gay optimism extended to Paris for the Fourth International Neurological Congress. There at the Rotisserie Perigourdine on the left bank of the Seine, 61 members and guests convened for an Academy banquet. Among distinguished guests were Profs. Alajouanine and Garcin from Paris, Prof. G. H. Monrad-Krohn (Oslo), and Sir Charles P. Symonds (London).... In this formative year, many eminent neurologists of an older school rallied to support the AAN. Among them were Foster Kennedy, Walter F. Schaller, Edwin G. Zabriskie, F. H. Lewy, Robert Wartenberg, and G. H. Monrad-Krohn.

Year of Program Orientation 1950

The next phase of AAN history produced a spontaneous evolution of basic principles to serve as guidelines for programming in the years to come: the two-year presidency and other high offices were not to be regarded as awards for scientific achievement, but rather as opportunities for those suitably endowed to guide a program toward the advancement of neurology on all fronts; the interests of the younger members, the lifeblood of the AAN, were to be respected, cultivated, and advanced wherever possible; a journal, an official publication for the Academy, devoted exclusively to clinical and basic neurology, was to be established. Moreover, members were to support promising neurologic programs of government agencies and institutes and serve on medical advisory boards of voluntary health agencies. Finally, the longitudinal axis of AAN membership was to be extended to include distinguished senior neurologists in North America (honorary members)[1], eminent neurologists in other countries (honorary-corresponding members), and clinicians and researchers of promise or distinction in related fields (associate members).... Though these prevailing guidelines were not developed into objective counterparts until 1951, the silhouettes of a few became visible at the annual meeting in Cincinnati (April 14-15, 1950). The editorial board of the projected AAN publication, NEUROLOGY, was appointed, with Russell N. DeJong serving as editor-in-chief and Webb Haymaker as associate editor. AAN members became active participants in the neurologic programs of the Veterans Administration and in their support of the National Institute of Neurological Diseases and Blindness authorized by Congress in 1950. A tower of strength in the latter sphere was H. Houston Merritt, cur-

[1]The first honorary members were elected in 1950: Carl D. Camp, George B. Hassin, Foster Kennedy, Lewis J. Pollock, A. T. Rasmussen, and C. E. VanEpps. . . . Elected later were: J. B. Ayer, Louis Casamajor, Stanley Cobb, Alexander Forbes, Wilder Penfield, H. R. Viets, and Philip Zenner.

rently president of the American Neurological Association, founded in 1875, and vice-president for the U.S.A. at the Sixth International Neurological Congress.

Year of Emergence 1951 The emergence of programs from principles began in 1951. The Journal NEUROLOGY first appeared in January, incorporating the NEWSLETTER as "the yellow pages." Its success was immediate, thanks to the sagacity of the editorial board and the personal interest of Publisher Louis M. Cohen[2], who procured as managing editor, attractive, capable Margaret M. Kane.... Also in 1951, Pres. Baker inaugurated the first (neuropathology) of a series of intensive review courses in specialized neurological disciplines. During the same year the program of the National Institute of Neurological Diseases and Blindness (NINDB), with which AAN activities are closely linked, was first activated. Other significant events were the organization of a committee on neurologic education under Russell N. DeJong, who pressed the need for growth in this field before the Association of American Medical Colleges (Oct. 23-25, 1950), and the appearance of the first roster of honorary-corresponding members[3]...Therefore, 1951 was a year devoted to program activation and growing strength, clouded only by the death of F. H. Lewey (Oct. 5, 1950).

Progress on Parade 1952-1957 The next four years witnessed a rising growth and momentum of activity at the AAN annual meetings as they swept from Virginia Beach (1951) to Louisville in 1952 (Pearce Bailey, 2nd pres.), to Chicago in 1953 and Washington, D. C., in 1954 (Howard D. Fabing, 3rd pres.), to Houson, Texas, in 1955 and St. Louis in 1956 (Walter O. Klingman, 4th pres.), and to Boston in 1957.... To administer this expansion, a full-time executive secretary, Mrs. J. C. McKinley, was appointed in 1952, with executive offices now at 3501 East 54th St., Minneapolis 17, Minn. During this period, attendance of members at annual meetings spiralled from 200 in 1949 to over 700 in 1957; scientific presentations, from 24 in 1949 to 193 in 1957. The activities of AAN committees increased and new ones were formed. From 1951 to 1957, the number of special review courses increased from two to ten and the number of registrants from 50 to 400. The Committee on Education (Francis M. Forster, Chairman) became a joint committee with representatives from the American Neurological Association in 1954 to conduct symposia on training of neurologists. The Committee on Research (A. S. Rose, chairman) introduced at annual meetings symposia of inquiry (cerebral vascular disease-1955, pyramidal tract--1956, and muscle disease--1957). Among new committees created were those of epidemiology (Lawrence C. Kolb and Leonard T. Kurland), international collaboration (Pearce Bailey), and registry for placement of neurologists (Maynard M. Cohen).... In 1952 a special

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[2]Mr. Cohen is president of Lancet Publications and publisher of Modern Medicine and Geriatrics.

[3]Nils Antoni, A. Austregesilo, A. Asenjo, A. Feiling, R. Garcin, K. Henner, Knud Krabbe, T. de Lehoczky, L. de Lisi, E. Moniz, G. H. Monrad-Krohn, Mme. Sorrel-Dejerine, A. H. Schroeder and M. O. Uzman. . . . In 1952, I. S. Aksel, D. Couto, Macdonald Critchley, L. Ibor, F. Luthy, G. W. Sillevis Smitt, Charles P. Symonds, F. M. R. Walshe; 195: R. Arana-Iniguez, F. Bremer, V. M. Buscaino, J. Chandy, H. H. Dale, E. Frauchiger, H. Gastaut, Y. H. Guinena, L. Halpern, W. R. Hess, H. Hoff, S. Katsunuma, A. Lima, H. F. Moran, A. Opalski, J. Pereyra-Kafer, G. G. J. Rademaker, S. Refsum, C. M. de Rojas, G. Schaltenbrand, E. Tchehrazi, J. O. Trelles, L. van Bogaert, K. Winther, and G. Wohlfart.

AAN committee created the National Committee for Research in Neurological Disorders (A. B. Baker, chairman), amalgamating into a single interagency committee six voluntary health organizations[4], each dedicated to a specific neurologic disability, in order that they might perform most effectively for the support of neurologic research programs when a united front was needed. Since then, three additional societies have joined the group[5].... Keeping apace was the journal NEUROLOGY. It began as a bi-monthly in 1951, became a monthly in 1953, and added an extra 16-page section. Subscriptions mounted from 1,640 in 1952 to about 4,000 in 1957. New sections were introduced on pediatric neurology, treatment reviews, and clinical pathologic conferences. H. Houston Merritt and Roland P. Mackay were added to the editorial board in 1954. NEUROLOGY has twice been awarded a Certificate of Excellence by the American Institute of Graphic Arts.

Crossfertilization 1956-1957 To the productive fertilization and maturation of AAN activities via its central core--medical neurology--there was added in 1956 a new growth aimed to broaden the AAN horizon. The impact of a rising generation of basic neurologic scientists and of clinicians with a specialized interest in the nervous system, indicated a need for crossfertilization of the diverse talents in the entire neurologic spectrum so as to create an inclusive body of neurologic scientists. This new project began by enlarging the category of associate members. Since the St. Louis meeting in 1956, 800 new members have been enrolled, of which over 500 are associates. A new section on neurochemistry was organized and presented a program at the 1957 Boston meeting; a section on neuroanatomy is being formed. The total AAN membership now approximates 2,000.... The surge of a new group of members with more diverse interests, of course, poses new program problems. Curiously, however, new problems in Academy growth seem to bring new solutions which lead to achievements, promising a better future for neurologic patients.

Brussels Reunion In the light of this background and spirit, Pres. Francis M. Forster and 200 AAN members from the U. S. and Canada have registered for the Brussels Congress, to participate in its scientific sessions and social events and to mingle with their fellow members and colleagues from other lands.... The Brussels Congress also has a special meaning; it is the first international congress in which the Academy has the honor to send an official delegate by invitation from the Executive Committee through the Secretary-General, Dr. Ludo van Bogaert.

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[4]National Epilepsy League, United Cerebral Palsy Associations, National Multiple Sclerosis Society, Committee for Public Understanding of Epilepsy, Muscular Dystrophy Associations, and National Society for Crippled Children and Adults.

[5]National Foundation for Infantile Paralysis, Association for the Aid of Crippled Children, and National Association for Retarded Children.

Roger I Bailey

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This is a normal myelogram in which ***Pantopaque Contrast Medium*** outlines the lower lumbar subarachnoid space and the sacral cul-de-sac. It is an anteroposterior radiograph made with the spot-film device after tilting the patient to the semierect position on the fluoroscopic table. This is to be compared with the myelogram at the right showing herniation of the fifth lumbar intervertebral disk.

The left lateral aspect of the ***Pantopaque*** column in the subarachnoid space is smoothly indented at the level of the fifth lumbar-first sacral intervertebral space. The left nerve root is not filled, while the right sheath is well visualized.

"PANTOPAQUE" *is the registered trademark under which all leading x-ray dealers supply the compound ethyl iodophenylundecylate, which is synthesized by the Research Laboratories of Eastman Kodak Company and prepared as the myelographic contrast medium Iodophenylate Injection, U.S.P., by Lafayette Pharmacal Company. The trademark serves to indicate to the radiologist continuity of experience in the manufacture of this medium.*